The Synthesis of *C*-Glycosides and Higher Monosaccharides Employing 1,3-Dipolar Cycloaddition Chemistry

Keith G. M^cMillan

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The University of Edinburgh

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The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
And I must follow, if I can,
Pursuing it with eager feet,
Until it joins some larger way,
Where many paths and errands meet.
And wither then? I cannot say.

The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
And I must follow, if I can,
Pursuing it with weary feet,
Until it joins some larger way,
Where many paths and errands meet.
And wither then? I cannot say.

The Road goes ever on and on
Out from the door where it began.
Now far ahead the Road has gone,
Let others follow it who can!
Let them a journey new begin,
But I at last with weary feet
Will turn towards the lighted inn,
My evening-rest and sleep to meet.

J. R. R. Tolkien
The Lord of the Rings

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Glossary of Terms, symbols and Abbreviations

δ	chemical shift
[α]	optical rotation
Ac	acetate
Bn	benzyl
Bz	benzoyl
d	doublet
DAH	3-deoxy-D-*arabino*-2-heptulosonic acid
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DMAD	dimethylacetylene dicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethyl-formamide
DMSO	dimethyl sulphoxide
ECF	ethyl cyanoformate
Ether	diethyl ether
FAB	fast atom bombardment
HOMO	highest occupied molecular orbital
J	coupling constant
KDN	3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid
KDO	3-deoxy-D-*manno*-2-octulosonic acid
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet
m/z	mass to charge ratio
M^+	molecular ion
Me	methyl
Ms	methanesulphonyl
MTAD	4-methyl-1,2,4-triazoline-3,5-dione
q	quartet
Ra Ni	Raney Nickel
s	singlet
t	triplet
THF	tetrahydrofuran
tlc	thin layer chromatography

Abstract

1,3-Dipolar cycloaddition chemistry has been employed in the production of a series of higher monosaccharides and *C*-glycosides. Two approaches were used; the first involved the cycloaddition of nitrile oxides to a series of sugar-derived alkenes, the second required the generation of pyranosyl nitrile sulphides from readily available precursors.

The sugar-derived alkenes were prepared using three methods; in the first hex-5-enofuranoses were generated in good yields from the corresponding 5,6-dimesylates using Tipson-Cohen conditions; the second employed an aprotic Bamford-Stevens reaction to give the 1-methylene sugar from the analogous pyranosyl tosylhydrazone. The final approach gave a series of 1-methylene sugars in moderate to good yields (50-82%) by the methylation of sugar lactones with dimethyl titanocene (Petasis Reagent).

The reactions of the nitrile oxides, R–C≡N^+–O^- (R = Ph, CO_2Et, Br) with 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**58**) gave 2-isoxazolines (4,5-dihydroisoxazoles, 67-69%) with π-facial selectivity for the newly formed stereocentre at the 5-position (5*R*:5*S* ≅ 85:15). Attempted hydrogenolysis of the cycloaddition products afforded only the unreacted starting material.

The 1,3-dipolar cycloaddition reactions of the nitrile oxides with the 1-methylene sugars gave spiroisoxazolines in moderate to good yields (42-82%), with a high degree of stereoselectivity (>95:5). The structures of these cycloadducts were established, by nOe experiment and x-ray crystallography, to be in the α-anomeric form.

The spiroisoxazolines resulting from the cycloadditions with the 1-methylene sugars were reductively cleaved employing hydrogen and Pearlman's catalyst, to give the corresponding γ-amino alcohols, in good yields (89-95%) as a mixture of isomers.

The enamines *N*-benzyl-2-methylene-pyrrolidine (**153**) and *N*-benzyl-2-methylene-piperidine (**154**) were generated from *N*-benzyl-2-pyrrolidone and *N*-benzyl-2-piperidone (**155**), respectively, by reaction with the Petasis reagent. Cycloaddition with benzonitrile oxide gave 6-benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene (**159**) and 6-benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (**160**), respectively, in moderate yields over two steps (23-24%) The products were characterised by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy.

The D-glucose derived enamine *N*-Boc-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**60**) was synthesised from *N*-Boc-2,3,4,6-tetra-*O*-benzyl-D-glucono-δ-lactam (**178**) by methylation with the Petasis reagent. Cycloaddition with benzonitrile oxide gave (5*R*,7*S*,8*R*,9*S*,10*R*)-*N*-Boc-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (**186**) as a single isomer.

A variety of conditions were employed to generate pyranosyl nitrile sulphides by thermal decarboxylation of 5-pyranosyl-1,3,4-oxathiazol-2-ones. The oxathiazolones, which were prepared by treatment of the corresponding amide with chlorocarbonylsulphenyl chloride, showed unusually high thermal stability. Heating 5-(1',2',3',4'-tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (**204**) in mesitylene (162-164°C) with ethyl cyanoformate resulted in the formation of the corresponding pyranosyl nitrile together with traces (1%) of ethyl 3-(1',2',3',4'-tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (**213**). When a similar reaction was carried out in a microwave reactor, starting material was recovered, although a small amount of ethyl 3-(1',2',3',4'-tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (**213**) was identified.

Table of Contents

1. Introduction

1.1 Foreword

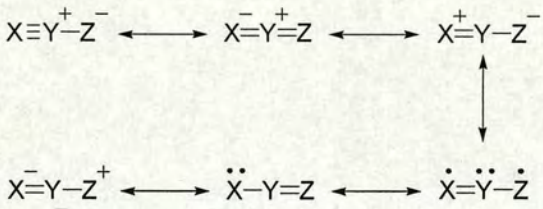
Higher monosaccharides are monosaccharides with a backbone of greater than six carbon atoms. They are rare in Nature, but are found as monomer units of some biopolymers.[1] This, along with their potential as non-toxic inhibitors of biosynthetic pathways, makes higher monosaccharides attractive synthetic targets.[2]

The work presented in this thesis examines the feasibility of synthesising higher monosaccharides and *C*-glycosides from readily accessible monosaccharides using 1,3-dipolar cycloaddition chemistry, eg nitrile oxide, nitrile sulfide and nitrone chemistry. These routes allow predictable and repeatable stereoselective extension of the carbon chain. It is anticipated that this will allow access to heptoses and octoses including ulosonic acid and deoxynojirimycin analogues and various *C*-glycosides.

1.2 1,3-Dipoles

1.2.1 What is a 1,3-Dipole?

A 1,3-dipole is a system where four π-electrons are delocalised over three atoms.[3] The origin of the name is twofold, firstly the dipole term originates from the inability to produce a resonance structure over the three atoms, without charges, where the electron requirement of each of the three atoms is satisfied (Scheme 1.1). The "1,3" term refers to the points of bonding to the dipole by some dipolarophile, rather than the localised positions of the charge.[3]



Scheme 1.1

There are two principle types of 1,3-dipole (Table 1.1), firstly the allyl type (Figure 1.1) that contains a double bond and where the central atom is sp^2 hybridised. The double bond that is present in this type of 1,3-dipole results in it having a bent structure. Secondly, there is the propargyl-allenyl type (Figure 1.2); this contains a third bond that is orthogonal to the second resulting in the central atom being sp hybridised. The structure is, therefore, linear.[3]

Table 1.1: Examples of 1,3-Dipoles

Allyl type			
Azomethine Betaines		Carbonyl Betaines	
R_2CNRCR_2	Azomethine Ylides	R_2COCR_2	Carbonyl Ylides
R_2CNRNR	Azomethine Imides	R_2CONR	Carbonyl Imides
R_2CNRO	Nitrones	R_2COO	Carbonyl Oxides
Propargyl-allenyl type			
Nitrilium Betaines		Diazonium Betaines	
RCNO	Nitrile Oxides	$NNCR_2$	Diazoalkenes
RCNNR	Nitrile Imides	NNNR	Azides
$RCNCR_2$	Nitrile Ylides	NNO	Nitrous Oxide
RCNS	Nitrile Sulfides	NNS	Dinitrogen Sulfide

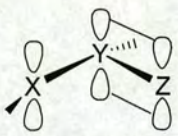


Figure 1.1

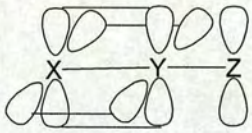


Figure 1.2

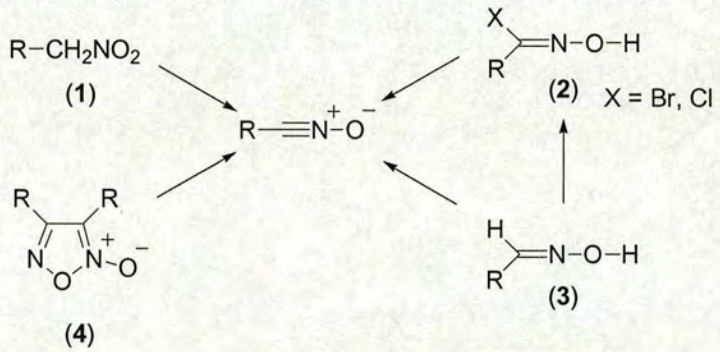
1.2.2 Properties of 1,3-Dipoles

The most important property of 1,3-dipoles is their ability to undergo 1,3-dipolar cycloaddition reactions with dipolarophiles. The reactivities of 1,3-dipoles are dependent upon the atoms present, which alter the energy levels of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).[3]

1.3 Nitrile Oxide Chemistry

1.3.1 Generation of Nitrile Oxides

There are a number of possible methods to obtain nitrile oxides.[4] The most common routes are dehydration of a primary nitroalkane (**1**) using eg phenyl isocyanate with a catalytic amount of triethylamine to produce a nitrile oxide, commonly known as the Mukaiyama method,[5] and dehydrohalogenation of a hydroximoyl halide (**2**) using triethylamine.[3,4] Other dehydrohalogenation agents employed are Na_2CO_3, Al_2O_3 and alkali metal fluorides.[4] A variety of methods have been used to halogenate the oxime, these will be discussed later. Another option is to convert the aldoxime (**3**) directly to the nitrile oxide in a one-pot reaction; this may be achieved using alkaline sodium hypochlorite[6] or hypobromite[7] and chloramine-T.[8] Lead tetraacetate has also been utilised for the dehydrogenation of *syn* aldoximes.[9] Another potential route is the thermal cycloreversion of the nitrile oxide dimers, 1,2,5-oxadiazole *N*-oxides (furazan *N*-oxides, furoxans, **4**) (Scheme 1.2).[4]

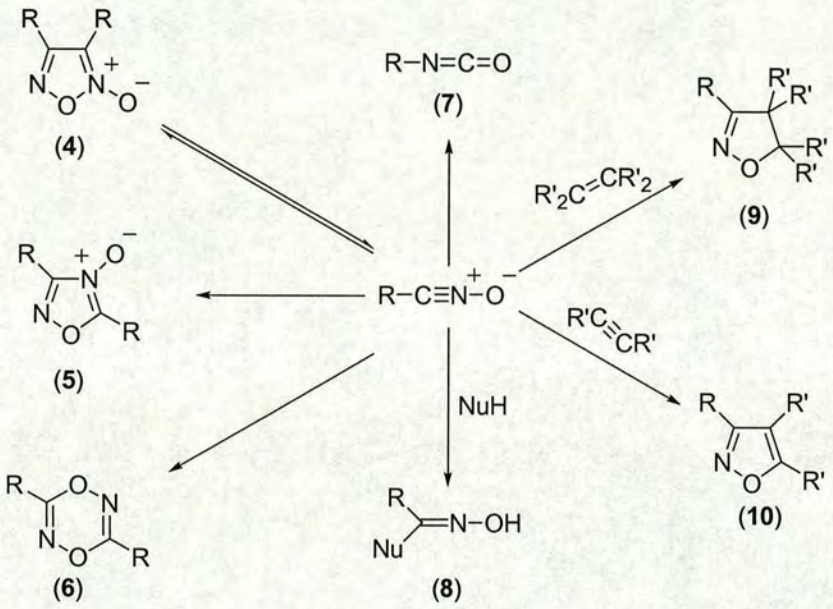


Scheme 1.2

1.3.2 Reactions and Reactivity of Nitrile Oxides

Once generated, there are a number of reactions that nitrile oxides may undergo (Scheme 1.3); which reactions occur is dependent upon what is present in the reaction mixture as well as the nitrile oxide being used. One consequence of the high reactivity of nitrile oxides is their tendency to dimerise to give the furoxan (**4**).[3,4] Alternative dimerisation pathways may also take place to give 1,2,4-oxadiazol-4-oxides (**5**) and 1,4,2,5-dioxadiazines (**6**).[3,4] The formation of the dimers is dependent upon the half-life of the nitrile oxide, which varies from seconds to minutes for aliphatic nitrile oxides to several hours or days for some aromatic nitrile oxides.[4] Some stable nitrile oxides have been shown to thermally rearrange

to give isocyanates (**7**), while nucleophilic addition gives substituted oximes (**8**).[4] Finally, nitrile oxides may undergo cycloaddition reactions with dipolarophiles such as alkenes and alkynes to afford isoxazolines (4,5-dihydroisoxazoles, **9**) and isoxazoles (**10**) respectively.[4]



Scheme 1.3

Reactivity in 1,3-dipolar cycloaddition reactions of nitrile oxides is dependent upon the nature of the reactants involved, as discussed by Sustmann.[10,11] The cycloaddition reactions of nitrile oxides were classified into three types. Type I reactions are those which involve electron rich dipoles, that is to say the nitrile oxide contains an electron donating group, which results in the frontier orbitals of the dipole being high in energy. The cycloaddition reactions of these nitrile oxides are described as being HOMO controlled or nucleophilic. This type of behaviour can be enhanced be adding electron donating groups to the dipole or electron withdrawing groups to the dipolarophile (Figure 1.3).[3,10] The second family of reactions are known as Type II; where the cycloadditions are both LUMO and HOMO–dipole controlled. These can involve either electron rich or electron poor dipolarophiles (Figure 1.3).[10,11] The final class of cycloaddition reactions are Type III; these nitrile oxides are electron deficient with low-lying frontier orbitals that favour interaction of the LUMO of the dipole with the relatively high energy HOMO of the dipolarophile.[10] As a result these nitrile oxides are electrophilic and their cycloadditions are LUMO controlled (Figure 1.3).[10]

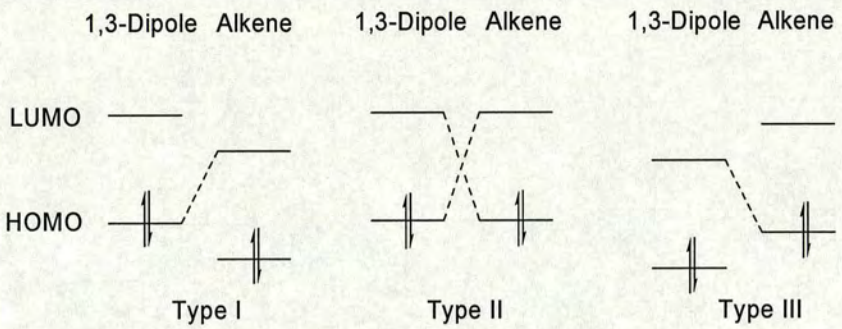
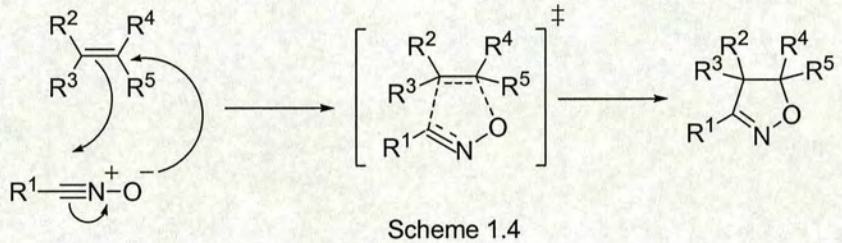


Figure 1.3

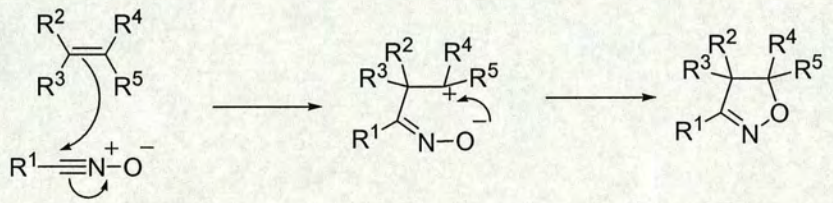
1.3.3 Mechanism of Nitrile Oxide Cycloadditions

Using the reaction of nitrile oxides with alkenes there are three possible mechanisms for the [3+2] cycloadditions; the first is a single step concerted process (Scheme 1.4).



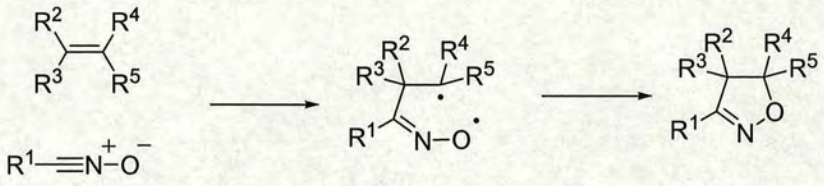
Scheme 1.4

The second is a stepwise, non-concerted, mechanism that involves a zwitterionic intermediate (Scheme 1.5).



Scheme 1.5

The final mechanism is again a non-concerted reaction, but with a diradical intermediate (Scheme 1.6).



Scheme 1.6

An important feature of the cycloaddition reaction between the 1,3-dipole and the alkene is that the configuration of the alkene is retained in the cycloadduct. This supports the concerted mechanism. However, if the mechanism involved a diradical or zwitterionic intermediate and the cyclisation were faster than the bond rotation the stereochemistry of the alkene would be retained. The concerted mechanism is also supported by the moderate activation energy and the large negative entropy of the reaction. However, some of the possible by-products of the cycloaddition reactions, such as oximes, can be explained by the existence of a diradical intermediate.[4]

It is generally accepted, however, that the cycloaddition of a nitrile oxide to a dipolarophile follows the concerted asynchronous [4π + 2π] suprafacial process as suggested by Huisgen (Scheme 1.4).[12,13]

1.3.4 Selectivity

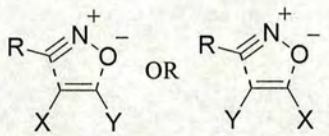


Figure 1.4

The regioselectivity of the cycloaddition of a nitrile oxide to an asymmetrically substituted alkene is determined by the stability of the respective transition states for the formation of two isomers (Figure 1.4), which is in turn dictated by the degree of overlap of the frontier orbitals of the two components.[3] This is set by the size of the coefficients such that the orbitals with the larger coefficients have the greater overlap. Therefore, the more stable arrangement is where orbitals with large coefficients are interacting and orbitals with small coefficients are interacting rather than those interactions of an orbital with a large coefficient and an orbital with a small coefficient (Figure 1.5).[3]

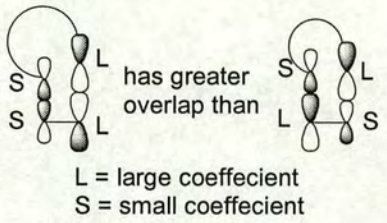


Figure 1.5

Also the smaller the energy difference between the HOMO and LUMO of the reactants the more stable the transition state.[3] This may be illustrated by the HOMO and LUMO interactions for the reaction between the electrophilic nitrile oxide, fulminic acid, and ethene with electronically different substituents (Figure 1.6).[3,4] This diagram shows that altering the type of substituent on the dipolarophile may affect the stability of the transition state. Electron donating groups destabilise the frontier orbitals of the dipolarophile and result in an increase in energy, thus favouring the dipole-LUMO/dipolarophile-HOMO interaction over the dipole-HOMO/dipolarophile-LUMO interaction. Conjugating groups on the dipolarophile have a similar effect on this reaction. Electron withdrawing groups attached to the dipolarophile result in a lowering in the energy of the HOMO and the LUMO. This favours dipole-HOMO/dipolarophile-LUMO interactions.

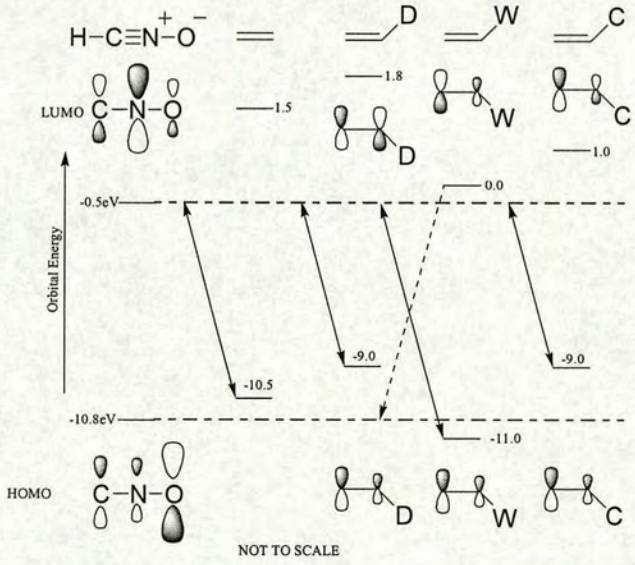
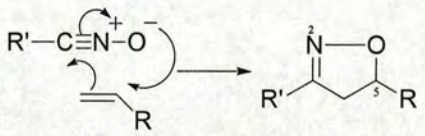


Figure 1.6

Figure 1.5 also illustrates the argument for the regioselectivity of the cycloaddition reaction between nitrile oxides and alkenes. It may be observed that the polarisation of the reactants

favours the 5-isomer in the most likely orbital arrangement of dipole-LUMO/dipolarophile-HOMO interactions.

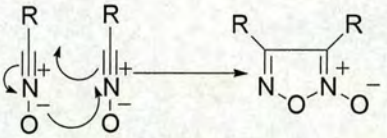
Reaction of a monosubstituted alkene with a nitrile oxide usually gives 5-substituted 2-isoxazolines (Scheme 1.7) in preference to the 4-substituted regioisomer. This is a result of the two effects discussed above. However, formation of the 4-substituted regioisomer is also limited by the large LUMO polarisation of the nitrile oxides.[3] Furthermore, steric effects result in the more electrophilic end of the dipole always bonding to the least substituted end of the alkene irrespective of this being the nucleophilic or the electrophilic terminus of the alkene.[3]



Scheme 1.7

1.3.5 Limitations of Nitrile Oxide Cycloadditions

One problem with the use of nitrile oxides in synthesis is their inherent reactivity and tendency to dimerise to give the corresponding 1,2,5-oxadiazole *N*-oxide (furoxan) (Scheme 1.8).[14]



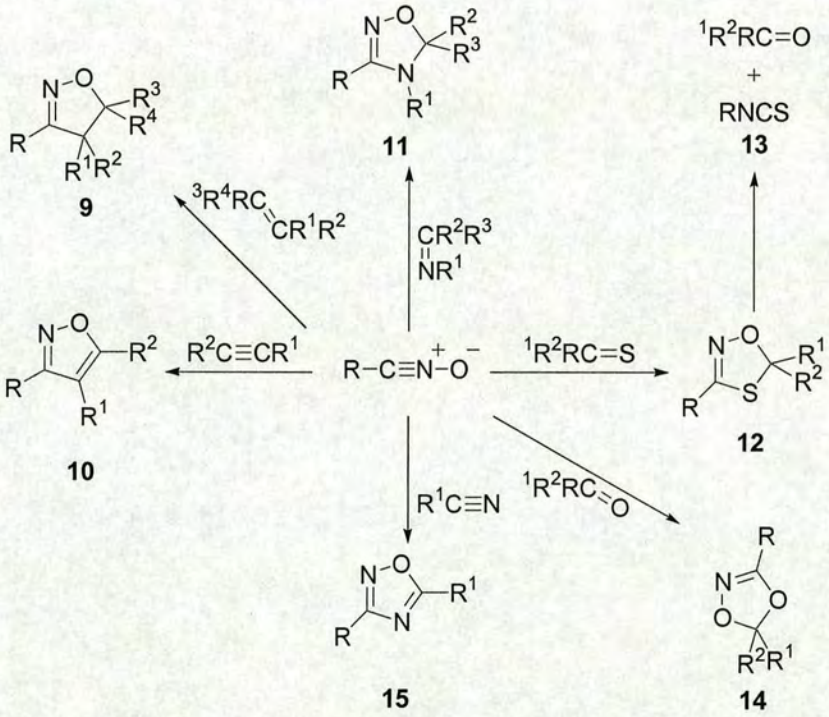
Scheme 1.8

Nitrile oxides have different half-lives; for example, aliphatic and acyl nitrile oxides are very reactive, while nitrile oxides containing aryl groups can have a half-life of several hours or days. As a result few nitrile oxides can be stored, and nearly all are produced *in situ* in the presence of excess dipolarophile for efficient cycloadduct formation.[4]

1.3.6 Synthetic Applications of Nitrile Oxide Chemistry

There are a number of cycloaddition reactions that nitrile oxides may undergo, other than those with alkenes and alkynes, to give various 5-membered heterocycles (Scheme 1.9), this reaction has long been used in the production of five-membered heterocycles containing a

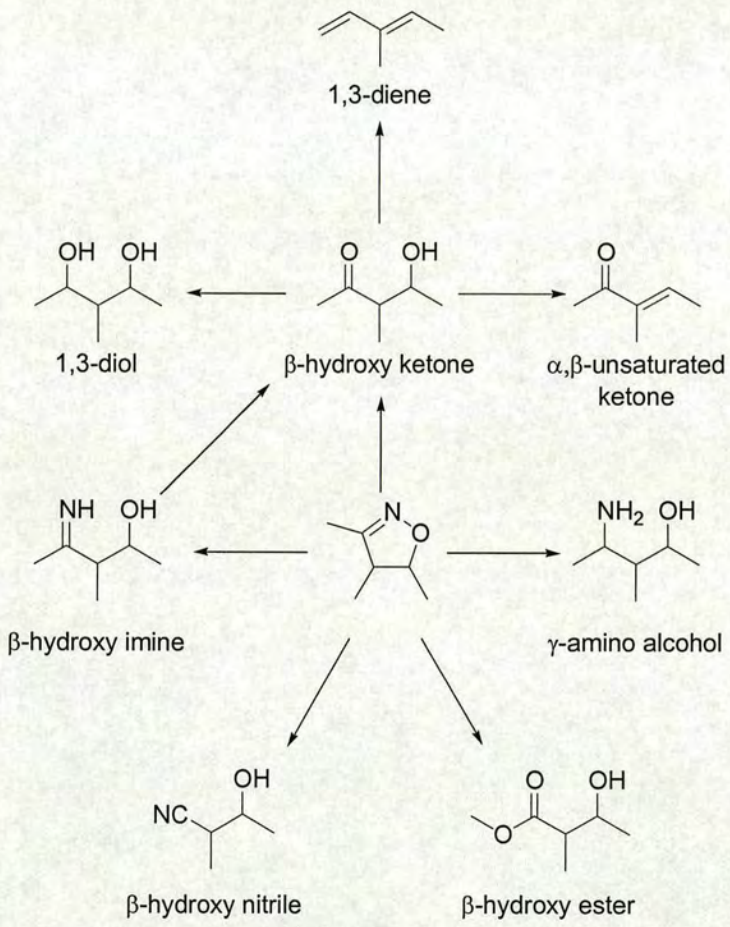
C=N–O group.[3] When a nitrile oxide is generated in the presence of an imine the heterocycle is known as a 1,2,4-oxadiazoline (**11**), the reaction between a nitrile oxide and thiocarbonyl affords a 1,4,2-oxathiazoline (**12**) that can decompose, on heating, to give the corresponding carbonyl compound and an isothiocyanate (**13**). This is a convenient way of converting thiocarbonyls to carbonyl compounds. Nitrile oxides also react with carbonyl compounds to give 1,4,2-dioxazoles (**14**) in the presence of a Lewis acid. Nitriles are generally poor dipolarophiles for nitrile oxide cycloadditions, however, when they do react they result in 1,2,4-oxadiazoles (**15**). Nitrile oxides have been known to cycloadd to other compounds containing unsaturated heteroatom bonds (e.g. R–C≡P, R–N=N–R), but some of these cycloadducts are too unstable to be isolated. These reactions are discussed in greater detail in the literature.[3]



Scheme 1.9

It has been known since 1894[15] that nitrile oxides react with alkenes to give 2-isoxazolines via 1,3-dipolar cycloaddition. Recently, however, these reactions have been directed toward the synthesis of a wider array of organic compounds. This broader use is due, in part, to the regio- and stereo-selective nature of 1,3-dipolar cycloadditions, as well as the mild nature of the reaction conditions.

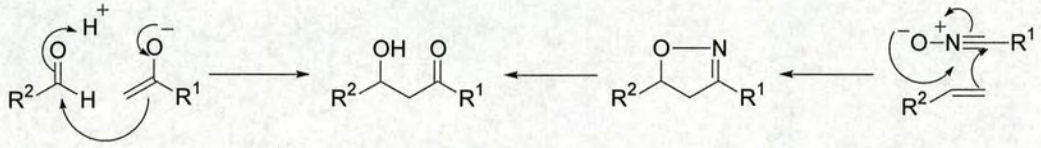
A major reason for using the nitrile oxide/isoxazoline approach is the stability of the isoxazoline ring when subjected to heat or when treated with acid, alkali or oxidising agents. An advantage of the stability of the isoxazoline moiety is that it allows the modification of substituents without affecting the ring system.[16,17] A further reason for employing this approach is the masked functionality contained within the isoxazoline ring (Scheme 1.10).[4,18] These functional groups can be released on reductive cleavage of the nitrogen-oxygen bond. A notable compound type accessible via the isoxazoline method is the β-hydroxy ketone, thus providing an alternative to the aldol reaction (Scheme 1.11).[16]



Scheme 1.10

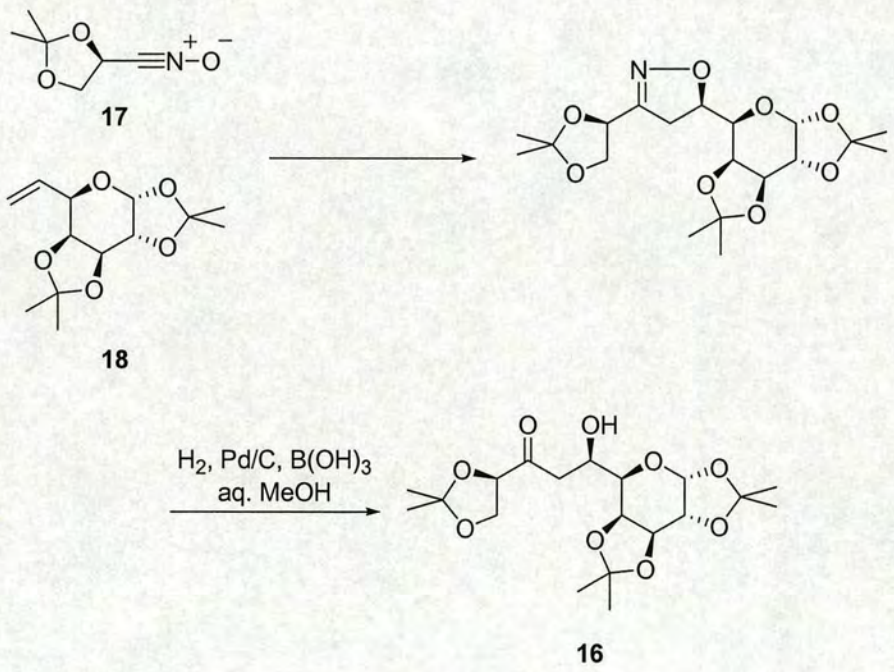
There are a number of problems associated with the aldol approach: it is a reversible reaction, and there can be side reactions to give cross- or self-aldol condensation products. The reaction has poor selectivity and there is also the problem of selective enolate formation.[19] The cycloaddition method provides an alternative approach which overcomes

some of these obstacles. The advantages of the nitrile oxide/isoxazoline method include the ability to easily produce stable precursors of nitrile oxides for [3+2] cycloaddition to an alkene. These reactions are performed under milder conditions, compared to the variety observed for the aldol reaction and its derivatives. Furthermore, the isoxazoline acts as a masked β-hydroxy ketone which can be released at any point in the synthetic sequence.[20] Finally, these cycloaddition reactions can be regio- and stereoselective.[14] Overall, the aldol and nitrile oxide methods are complementary approaches as they produce different carbon-carbon bonds within the product molecule (Scheme 1.11).



Scheme 1.11

Within our group this chemistry has been applied to a number of sugar systems as a method for chain extension to give higher monosaccharides.[14,17] This work utilised a variety of sugar-derived nitrile oxides and sugar-derived alkenes, an example of which is shown in Scheme 1.12. The nonose derivative **16** was prepared by combination of D-glyceronitrile oxide **17** and D-galactose-derived alkene **18** and ring opening of the cycloadduct.

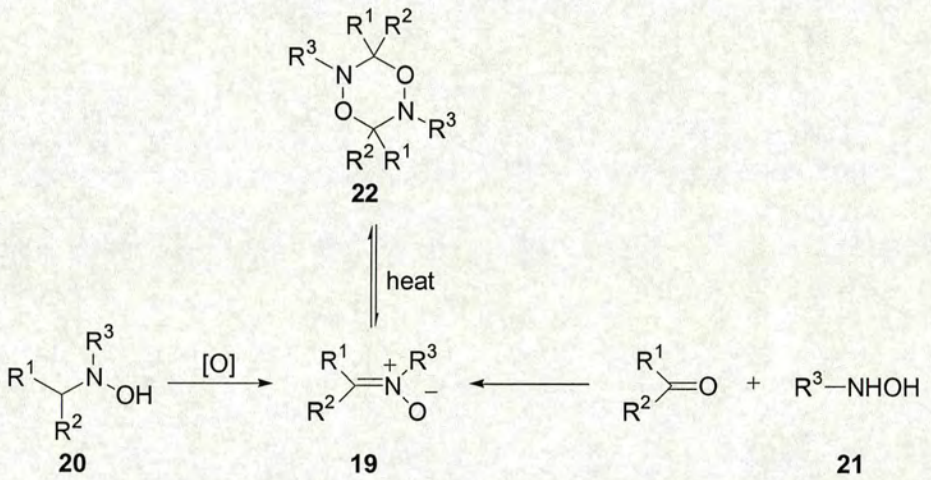


Scheme 1.12

1.4 Nitrone Chemistry

1.4.1 Generation of Nitrones

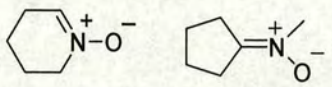
As with nitrile oxides the synthesis of azomethine oxides (nitrones) (**19**) has been extensively researched and there are a number of possible pathways for their generation.[3] *N*,*N*-Disubstituted hydroxylamines (**20**) can be oxidised to corresponding nitrones using various oxidising agents such yellow mercuric oxide, "active" lead oxide, potassium ferricyanide, potassium permanganate, I-butyl hydroperoxide and hydrogen peroxide.[21] Another method is the condensation of a hydroxylamine (**21**) with either an aldehyde or a ketone. The trimers and dimers (**22**) may be cracked to give relevant the nitrones (Scheme 1.13).[3]



Scheme 1.13

1.4.2 Reactions and Reactivity of Nitrones

There are varying reactivities over the nitrone family. Some are highly reactive, eg **23**, such that they self react to give the corresponding dimer and/or trimer, while others are relatively stable and may be isolated, for example **24**.[3]



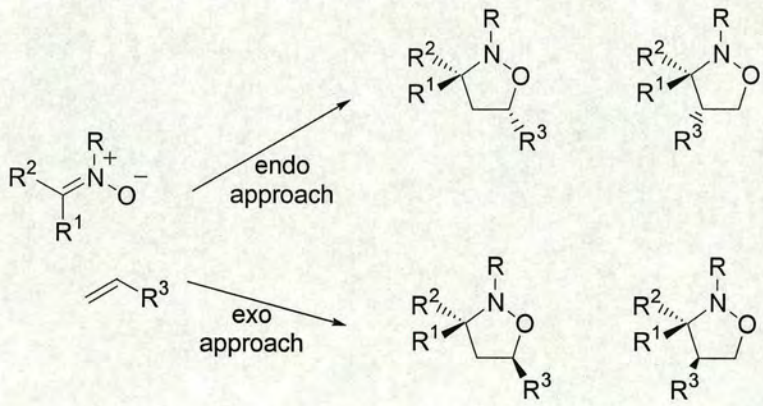
23 **24**

As with nitrile oxide chemistry, the reactivity of the nitrone analogues in 1,3-dipolar cycloadditions has been classified using the Sustmann model into three types with regard to the frontier molecular orbitals. Most nitrone cycloadditions are thought to involve Type II interactions. That is to say that they maybe both HOMO-dipole/LUMO-dipolarophile controlled and LUMO-dipole/HOMO-dipolarophile controlled.[3]

Similar to the nitrile oxide case, the cycloaddition of a nitrone to a dipolarophile is thought to be a concerted asynchronous [4π + 2π] suprafacial process[22] as the stereochemistry of the dipolarophile is retained in the resulting isoxazolidine cycloadduct[3] and the thermodynamics of the reaction correspond to those of a concerted process.[3]

1.4.3 Selectivity

The 1,3-dipolar cycloaddition between a nitrone and an alkene can give two pairs of regiomeric and diastereomeric isoxazolidines (Scheme 1.14) and can, depending upon the number of substituents on the alkene, generate two or three new stereocentres. For example reaction with monosubstituted alkenes will result in two new stereocentres while reaction with 1,2-disubstituted alkenes will produce three new stereocentres.[22]

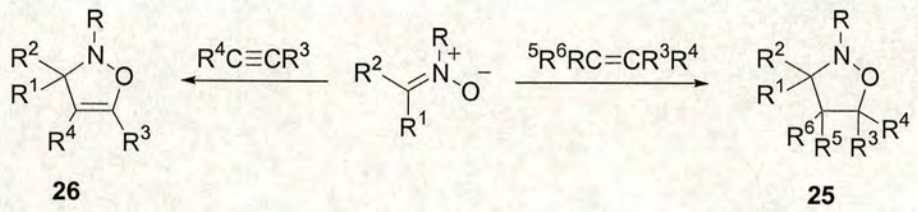


Scheme 1.14

The regiochemistry may be explained by the same reasoning as that given for the nitrile oxide cycloaddition in Section 1.3.5. The dominant regioisomers are those with the R^3 substituent in the 5-position of the isoxazolidine ring. This is due to the carbon of the nitrone and the unsubstituted carbon of the alkene having the largest atomic orbitals. Therefore, the interaction between these two atoms will provide the greatest overlap and hence the most stable transition state.[3] However, it is notable that for very electron deficient dipolarophiles the cycloaddition is a Type I process and the 4-substituted product is produced. This is due to the lowering of the HOMO and LUMO levels of the dipolarophile, to favour the HOMO-dipole/LUMO-dipolarophile interaction.[3]

1.4.4 Synthetic Applications of Nitrone/Isoxazolidine Chemistry

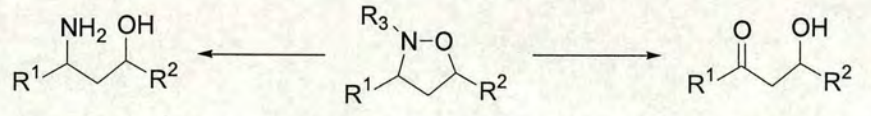
Nitrones may undergo a variety of cycloaddition reactions these have been extensively reviewed.[3] The reactions involving alkenes and alkynes giving isoxazolidines (**25**) and isoxazolines (**26**) respectively are of greatest relevance to this work (Scheme 1.15).



26 **25**

Scheme 1.15

The cycloaddition of nitrones to alkenes has long been a synthetic method for producing 5-membered isoxazolidines.[3] Isoxazolidines, like isoxazolines, have a number of synthetically useful masked functionalities that may be accessed by breaking the N-O bond, including γ-amino alcohols and β-hydroxy ketones (Scheme 1.16).[22] This chemistry allows an alternative to the nitrile oxide approach to these synthetically useful intermediates.



γ-amino alcohol β-hydroxy ketone

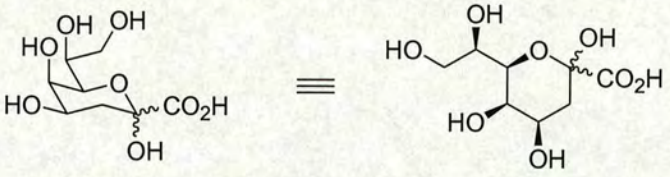
Scheme 1.16

As with nitrile oxides the propensity for certain nitrones to dimerise limits the use of this chemistry to very reactive dipolarophiles with these labile nitrones.[3]

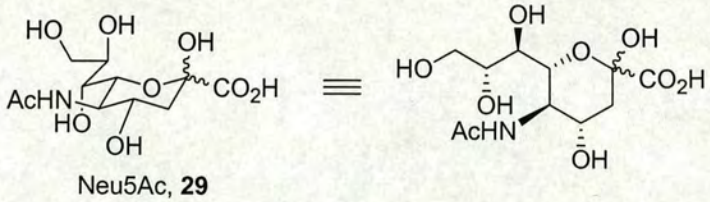
1.5 3-Deoxyulosonic Acids and Their Analogues

3-Deoxyulosonic acids and their analogues have a variety of roles within Nature and are important in a number of biological systems. They are, therefore, important synthetic targets.

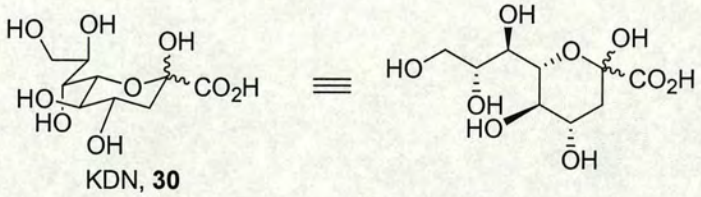
DAH, **27**



KDO, **28**



Neu5Ac, **29**

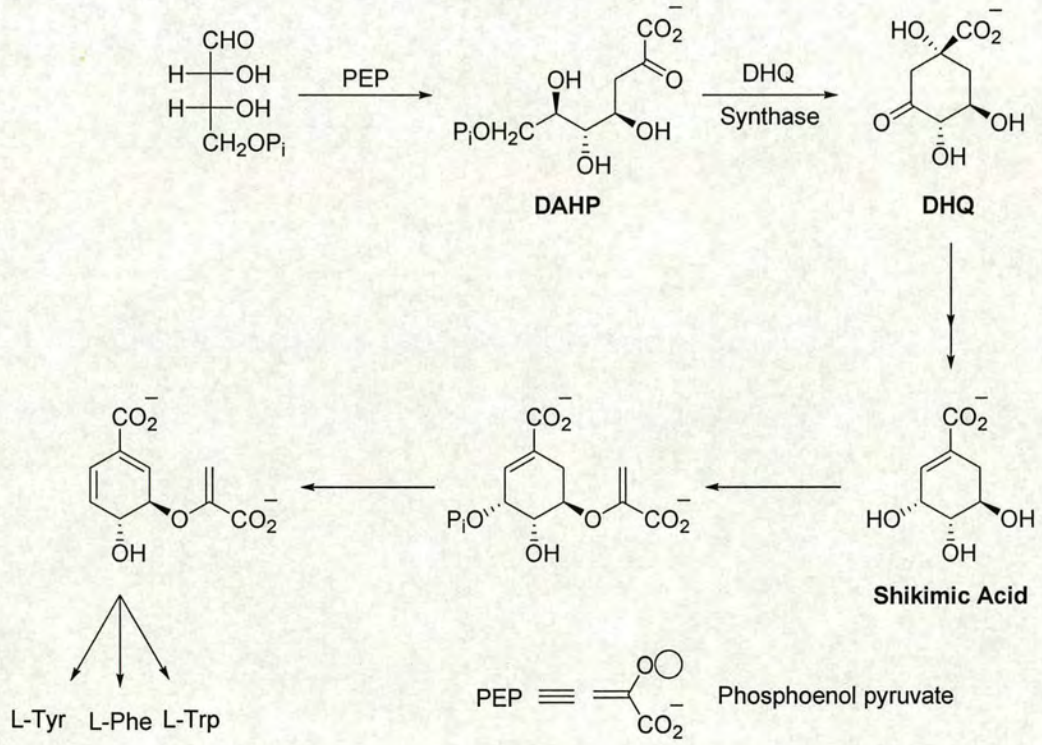


KDN, **30**

Four examples of ulosonic acids are shown below. 3-Deoxy-D-*arabino*-2-heptulosonic acid (DAH, **27**), is important in the shikimate pathway (Scheme 1.17). This is a biosynthetic process in higher plants and bacteria that produces the three aromatic amino acids tyrosine, tryptophan and phenylalanine.[19,23,24] Inhibition of this pathway offers potential for the design of herbicidal, fungicidal and bactericidal compounds.[25] There are a number of potential enzymes that may be targeted for inhibition through the synthesis of analogues of

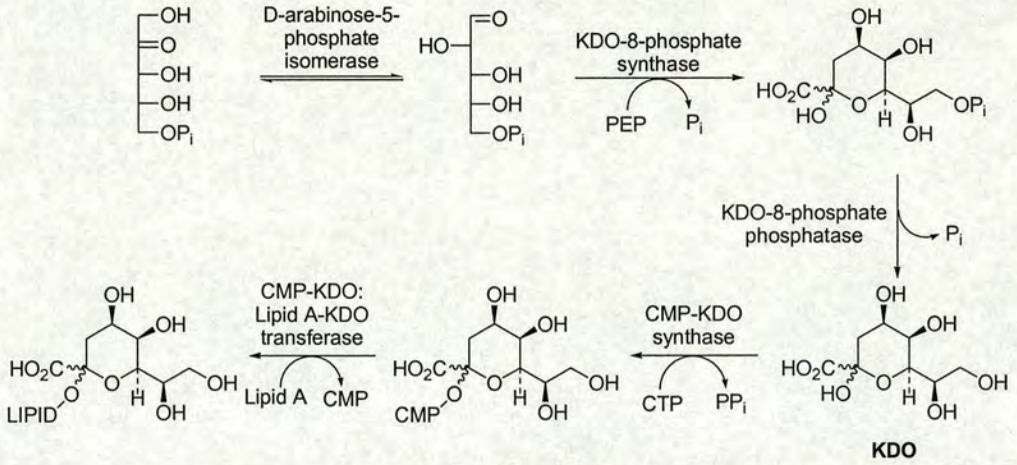
intermediate metabolites found in the pathway.[25] The specific enzyme that is targeted by the DAH analogues is the 7-phospho-3-deoxy-D-*arabino*-heptulosonate phosphate lyase (3-dehydroquinate synthase), which catalyses the ring closure of DAHP to form the first alicylic in the pathway.[25] 3-Deoxy-D-*manno*-2-octulosonic acid (KDO, **28**) is an eight-carbon ulosonic acid that is required for the replication of all Gram-negative bacteria. The importance of this saccharide is due to the core sugars of Gram-negative bacteria being linked to lipid A by KDO. The absence of this linker causes the structural and functional integrity of the outer membrane to be compromised. Therefore the incorporation of KDO into lipid A (Scheme 1.18) it is critical to the cell replication.[26] As with the Shikimate pathway, there are several possible enzymes in this pathway that are potential targets for inhibition. For example, CMP-KDO synthase, which links the KDO with cytidine-5-monophosphate to give α-cytidine-5'-monophosphate-KDO is a possible target for inhibition.[26]

The Shikimate Pathway



Scheme 1.17

The Incorporation of KDO into Lipid A



Scheme 1.18

N-Acetyl-5-amino-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (*N*-acetyl-neuraminic acid, Neu5Ac or NANA, **29**) is a nine-carbon sugar, which is a member of a group of compounds known as sialic acids. It is found in the nerve tissue and the cellular membrane of a number of mammals and bacteria, at the terminal positions of glycolipids, glycoproteins and oligosaccarides.[27,28] This acid is significant in biological molecular recognition processes such as differentiation phenomena and cell adhesion. The 5-deamino analogue, 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **30**) is found in the eggs of rainbow trout and is thought to be involved in their activation by protection against the action of sialidase.[29]

In Nature, the synthesis of higher ulosonic acids is thought to proceed via a stereoselective aldol condensation of the aldose with phosphoenol pyruvate (PEP) catalysed by the appropriate aldolase enzyme. A number of derivatives of the above compounds have been produced,[19] with a view to inhibiting critical steps in the biosynthetic pathways. This allows access to potential anti-bacterial drugs for use in chemotherapy from the KDO derived compounds and possible herbicides and anti-microbial agents to be obtained from the DAH analogues.[19] The major advantage of these compounds is that they provide a non-toxic means of inhibition of these pathways. This is due to neither the shikimate pathway nor the KDO pathway being vital for the survival of animal cells, while both are required by prokaryote and plant cells.[19,30] There are a number of published methods to synthesise the above compounds and their analogues. These include a tetrazole containing analogue of DAH that

was produced from D-mannose.[31] Neu5Ac has been previously synthesised by the chain extension of 1-deoxy-1-nitrohexose by the of addition *tert*-butyl 2-(bromomethyl)acrylate.[32] There have been many syntheses published for KDO analogues, both chemical and biological, for example the reduction of endoglycals[33] and enzymatic conversions,[34] respectively.

1.6 Iminosugars

1.6.1 Foreword

A logical extension of the exoglycal work is to explore the potential of iminosugars as dipolarophiles for cycloaddition reactions. Iminosugars are saccharides in which the ring oxygen has been replaced with a secondary amine.

1.6.2 Iminosugars and Their Mimics

The range of biological activity associated with iminosugars has been extensively reviewed[35] and they have been explored as potential biomedical agents, pesticides and ecological agents.

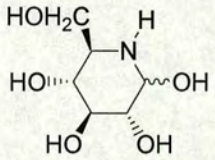
Iminosugars are known to inhibit glycosidase enzymes and can influence the glycosylation or catabolism of glycoproteins as well as inhibiting the recognition of specific carbohydrates.[36] This is due to their structural similarity to monosaccharides involved in glycoprotein processing.[35] Several studies have been carried out to identify the requirements for inhibition of glycosidases by basic sugar analogues. It was found that the following were necessary for successful inhibitors: 1) position of the basic (cationic) centre, 2) basicity, 3) geometry and charge distribution at the anomeric position, 4) hydroxylation pattern, ring size and flexibility as determinants of specificity, 5) interactions with the aglycon binding site and 6) hydrogen-bonding formation with the catalytic acid.[35]

Several plants contain iminosugars that are toxic to a number of important insectoid pests, e.g. *Locusta migratoria* and *Schistocera gregaria*. It is thought that this is due to the glycosidase inhibitory properties of the iminosugars. Iminosugars have also been proposed as potential nematicides.[35]

Iminosugars have also been proposed as potential plant growth inhibitors eg *Castanospermine* inhibits root elongation in dicotyledons.[35]

It is hoped to synthesise sugar mimics analogous to nojirimycin (**31**) and 1-deoxynojirimycin (**32**), which inhibit the human lysosomial trimming α-glucosidases and α-mannosidases. These enzymes are involved in the biosynthesis of the *N*-linked oligosaccharidic component of the membrane glycoproteins.[37,38] This inhibition stops the formation of the envelope

glycoprotein of HIV and the maturation of the oligosaccharide subunits of tumour cell glycoproteins, which are associated with possible malignancy.[37]



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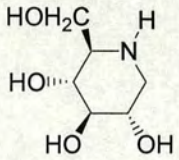


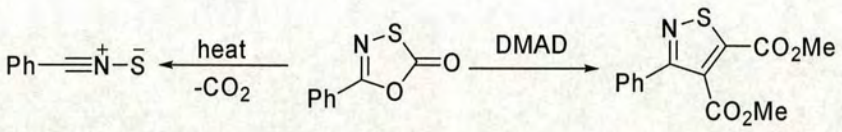
32

The reason for the importance of azasugars in glycosidase processes is that the hydrolysis of the glycosidic bond involves an intermediate oxonium ion,[37,39] which may be mimicked by replacing the oxygen with a basic nitrogen. This will allow the protonated azasugar to occupy the enzymatic active site, but not allow the continuation of the biological process.

1.7 Nitrile Sulfide Chemistry

1.7.1 Foreword

The existence of nitrile sulfides was first confirmed by Franz in 1970.[40] He observed that upon thermolysis of phenyl oxathiazolone (**33**) three decomposition products were generated, benzonitrile, sulfur and carbon dioxide.[41] It was thought that this decomposition would proceed via an intermediate nitrile sulfide, and this was confirmed by heating the oxathiazolone in the presence of dimethyl acetylenedicarboxylate (DMAD), which trapped the nitrile sulfide to give the isothiazole diester (**34**) (Scheme 1.19).[42]

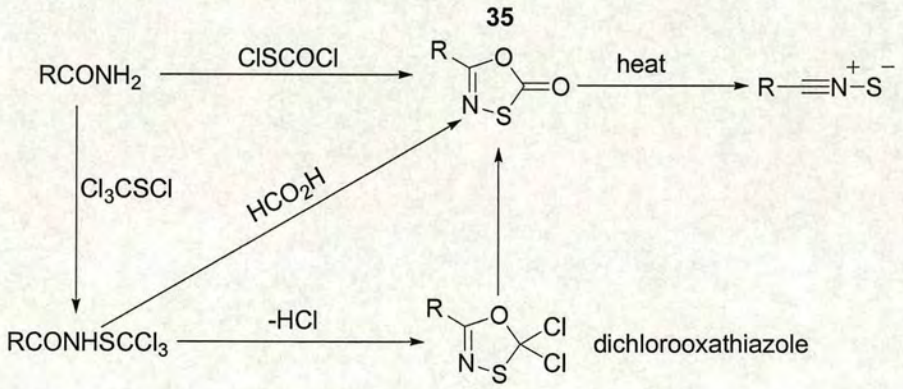


33 **34**

Scheme 1.19

1.7.2 Generation of Nitrile Sulfides

There are a number of methods for production of nitrile sulfides employing both thermolytic and photolytic techniques. The latter does not generate the nitrile sulfides in synthetically usable yields[43] and, as a result, has been used principally for matrix isolation and spectroscopic investigations.[42] Consequently photolysis will not be discussed here, though it has been extensively reviewed.[42,44] Here we shall only be concerned with generation of nitrile sulfides employing thermolytic methods.



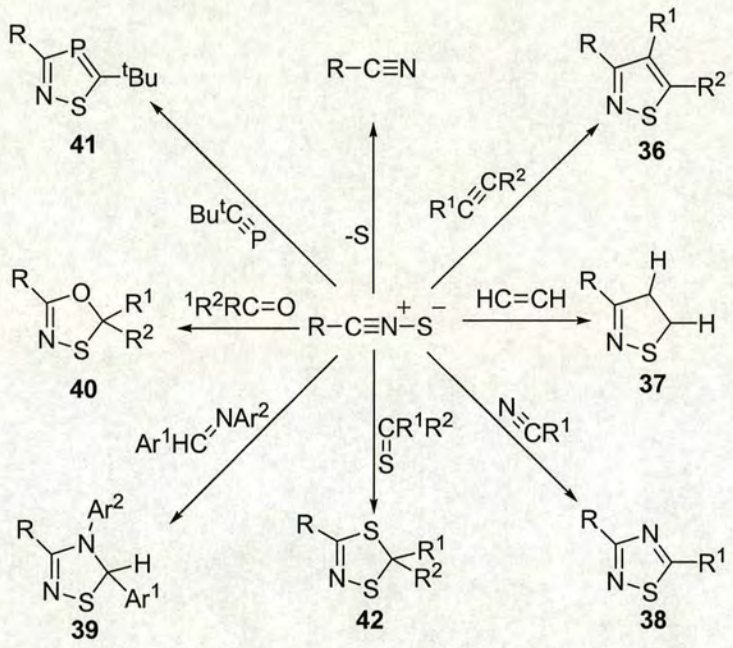
Scheme 1.20

The most used route to nitrile sulfides is the cycloreversion of 5-membered heterocycles that contain the C=N-S unit.[42] A common method (Schemes 1.20) is the decarboxylation of a 1,3,4-oxathiazol-2-one (**35**). This stable precursor may be synthesised from the corresponding carboxamide by heating with chlorocarbonylsulfenyl chloride,[45] or with perchloromethyl mercaptan followed by formic acid[41] or triethylamine.[46]

A major advantage of this method is that oxathiazolones may be synthesised with a variety of substituents in the 5-position including phenols,[47-49] esters,[47-51] nitriles,[43,52] alkenes,[53,54] sugars,[55,56] as well as simple alkyl and aryl groups.[42] However, nucleophilic substituents cannot be present as these would react with the oxathiazolone moiety.[57-59] The oxathiazolone is then heated between 110-160°C in an inert solvent, such as xylene or toluene, to generate the corresponding nitrile sulfide via thermal decarboxylation.[42]

1.7.3 Reactions of Nitrile Sulfides

Nitrile sulfides cannot generally be isolated, other than by matrix isolation techniques.[42] However, nitrile sulfides can react with a variety of functional groups yielding a plethora of new 5-membered heterocycles with variable substituents on the ring (Scheme 1.21). When an oxathiazolone is heated in an inert solvent in the absence of a dipolarophile the nitrile sulfide produced decomposes to the corresponding nitrile and sulfur. The reaction between nitrile sulfides and alkynes gives isothiazoles (**36**), that with alkenes results in 2-isothiazolines (**37**), whereas nitriles produce 1,2,4-thiadiazoles (**38**), as does the reaction with imines (**39**), carbonyl compounds give 1,3,4-oxathiazoles (**40**) and finally the reaction between nitrile sulfides and a phosphaalkyne yields a 1,2,4-thiazaphasphole (**41**).[42,44] Nitrile sulfides can also react with thiocarbonyl compounds to give 1,4,2-dithiazoles (**42**) in modest to good yields.[60] However, the reaction fails with dithio esters and tertiary thioamides; it only works when the substituents of the thiocarbonyl compound are diaryl, aryl alkyl and dialkyl thioketones and thiono esters.[61]



Scheme 1.21

1.7.4 Reactivity

As with nitrile oxides and nitrones, the reactivity of nitrile sulfide reactions may be rationalised using FMO theory. The HOMO and LUMO energy levels of nitrile sulfides are comparable to those of nitrile ylides; those of the former being only slightly lower in energy than those of the latter. This is due to the greater electronegativity of the sulfur.[42,43] As a result electron-poor acetylenic esters react with nitrile sulfides in HOMO dipole-controlled Sustmann Type II reactions.[42,43] Therefore, the rate of reaction increases as the electron deficiency of the dipolarophile increases, due to the lowering in energy of the dipolarophile LUMO. This gives the following reactivity profile for such esters with nitrile sulfides; DMAD>ethyl propiolate > ethyl phenyl propiolate > ethyl but-2-ynoate.[43]

1.7.5 Mechanism of Nitrile Sulfide Formation and Cycloadditions

The proposed mechanism of the nitrile sulfide generation, from the oxathiazolone, is accepted as following a decomposition pathway where the oxathiazolone loses carbon dioxide to give the corresponding nitrile sulfide.[43] Once produced the nitrile sulfide can undergo further decomposition to the nitrile through the loss of sulfur or it can react with a

dipolarophile to give a heterocyclic cycloadduct. The formation of both these products are first order and equal to that for the consumption of the oxathiazolone,[43] thus indicating that no adduct is formed between the oxathiazolone and the dipolarophile prior to the loss of carbon dioxide.[43]

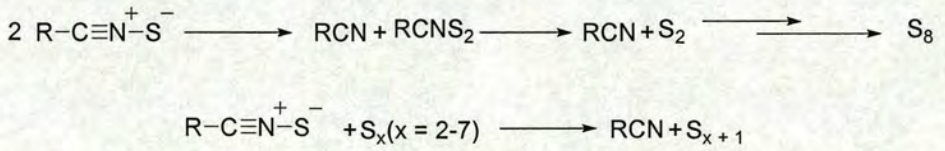
1.7.6 Selectivity

The regioselectivity of nitrile sulfide cycloadditions has been rationalised using CNDO/2 calculations;[42] these suggest that in the LUMO the largest orbital coefficient is affiliated to the carbon, while in the HOMO it is associated with the sulfur. The result of this is that 4-substituted products are formed from dipole-HOMO controlled reactions and the 5-substituted heterocycles will predominate in dipole-LUMO controlled reactions.[42] It has also been suggested that the high temperature at which nitrile sulfide cycloaddition reactions are carried out reduces the regioselectivity of the product.[42,43]

1.7.7 Limitations of Nitrile Sulfide Chemistry

The major drawback of nitrile sulfide chemistry is the tendency for the nitrile sulfide to decompose to the corresponding nitrile and sulfur before it can react with the dipolarophile.[42,44] Initially the nitrile sulfide decomposition reaction was thought to be unimolecular, however, it was observed that isolated nitrile sulfides were stable on an inert matrix and as soon as this support was consumed then the dipole would decompose. Furthermore, nitrile sulfide trapping reactions were found to be dilution dependent such that a reaction would give improved yields of the intended cycloadduct rather than the nitrile decomposition product, only when the nitrile sulfide was present at a low concentration.

These findings implied a higher order reaction and the following mechanism was proposed (Scheme 1.22).[42,44]



Scheme 1.22

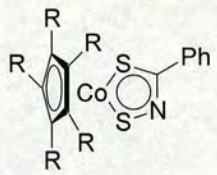
There have been a number of suggested approaches to combat this problem. The first way to lessen the decomposition is to ensure that the concentration of the nitrile sulfide is kept low.

This may be achieved either by adding the nitrile sulfide precursor portionwise,[54] or by having a large excess of the dipolarophile present.[42] It has also been noted that electron withdrawing groups on a nitrile sulfide reduce the rate of decomposition of the 1,3-dipole.[43] However, electron withdrawing groups have been reported to inhibit the cycloaddition reaction which is favoured by electron donating groups on the nitrile sulfide.[44]

1.7.8 Synthetic Applications of Oxathiazolone Chemistry

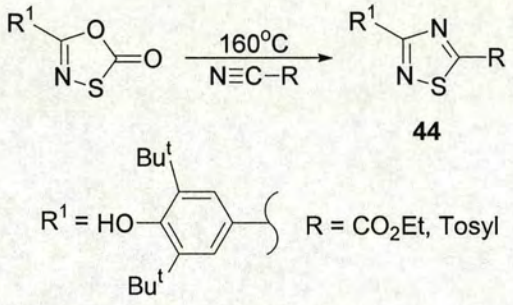
The initial interest in nitrile sulfide chemistry, with a view to biological applications, came in the early 1980's with the synthesis of *o*-(1,2,4-thiadiazoyl) benzoates as potential herbicides and plant growth inhibitors.[52] A variety of nitrile sulfide derived compounds have been synthesised and some have been found to have significant biological activity. Of particular interest are sugar derived heterocycles, as these *C*-nucleoside analogues have potential anti-tumour and anti-viral properties.[55] The enhanced biological stability of *C*-nucleosides is due to their resistance to hydrolysis of the glycoside linkage which is important with regard to anti-tumour activity.[55]

Oxathiazolones have been used in metal complex chemistry. A number of oxathiazolones have been used to insert sulfur into a manganese cluster by reaction between $[Mn(CO)_5]^-$ and a 5-substituted oxathiazolone (**35**), where R = phenyl, methyl or 3,5-nitrophenyl, to give the cluster $[Mn_3(CO)_9(\mu_3\text{-}S)_2]^-$.[63] There are also examples of oxathiazolone reaction products being used as ligands for transition metals. An example of this is a cobalt centred complex that was produced by the thermolysis of phenyl oxathiazolone **33** in the presence of $[Co(Cp)(CO)_2]$ to give 1,2,5,3-cobaltadithiazole (**43**).[64]



43

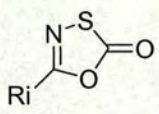
Nitrile sulfides have also been exploited in the synthesis of potential non-steroidal anti-inflammatory drugs, eg 1,2,4-thiadiazole (**44**) with 2,6-di-*tert*-butylphenol substituent (Scheme 1.23) in the 3-position.[65]



Scheme 1.23

In the case of 5-tosyl 1,2,4-thiadiazoles the labile tosyl group in the 5-position can be displaced by a large number of nucleophiles that allowed access to a variety of derivatives[66,67] of differing biological activities as potential inhibitors of both cyclooxygenase (CO) and 5-lipoxygenase (5-LO) activity as measured in rat basophilic leukaemia (RBL-1) cells.[66]

Furanosyl nitrile sulfide chemistry has been previously explored by Buffel *et al.*[55,56] He prepared a number of compounds from the oxathiazolone (**45**). The nitrile sulfide was trapped by DMAD to give the dimethyl 3-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-isothiazoledicarboxylate (**46**), which was then reacted further to produce compounds such as 4-amino-3-β-D-ribofuranosyl-5-isothiazolecarboxamide (**47**), 3-β-D-ribofuranosyl-isothiazolo[4,5-*d*]pyrimidine-7(6*H*)-one (**48**) and 4-amino-3-β-D-ribofuranosylisothiazole-5-carboxylic acid (**49**).



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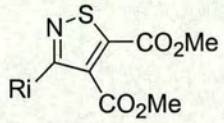

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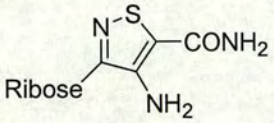

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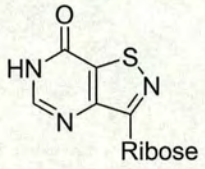

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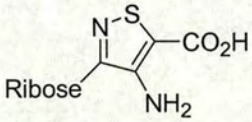

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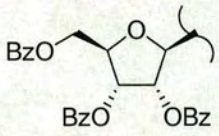
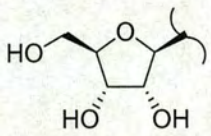
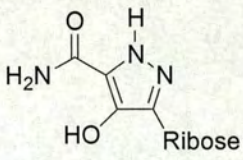


Ri =



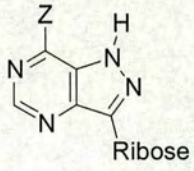
Ribose =

However, none of these compounds was found to have any biological activity despite the structural similarities to pyrazofuran (**50**) and formycin (**51**).



pyrazofuran

50



a: Z = NH_2 formycin A
b: Z = OH formycin B

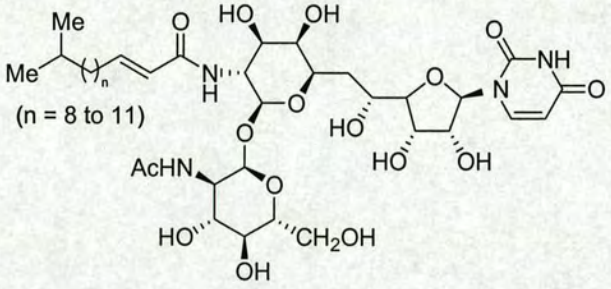
51

2. Results and Discussion

There are three related topics explored in this work; the first involves the development of the synthetic method for producing higher monosaccharides by the chain extension of various lower homologues, the second is to examine the potential of sugar-derived enamines as synthetic building blocks for higher monosaccharide analogues, and the final theme explores the synthesis of *C*-glycosides based on nitrile sulfide chemistry.

2.1 Introduction

Higher monosaccharides are of synthetic interest as they are less abundant in Nature than lower homologues and are involved in a number of biosynthetic pathways. They are possible targets for herbicidal, antifungal, antimicrobial and antibacterial agents. Examples of such higher sugars are the tunicamycins (**52**)[67] and the herbicidins (**53**).[68] Also of interest are DAH (**27**) and KDO (**28**) as discussed in Section 1.5. *C*-Glycosides are of synthetic value as they are resistant to hydrolysis of the glycoside linkage found in *O*-glycosides. These compounds have potential as glycosidase inhibitors, a number of which have been found in Nature.[69,70]



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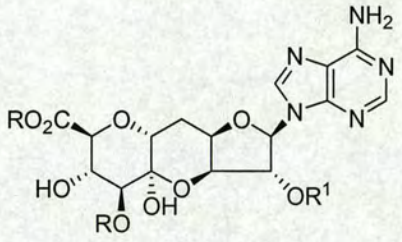

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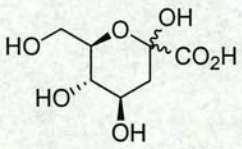
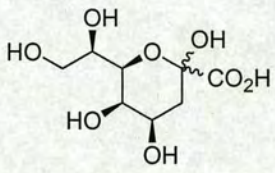


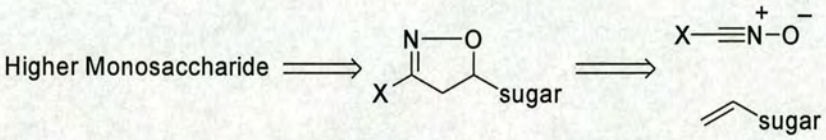
DAH, **27**



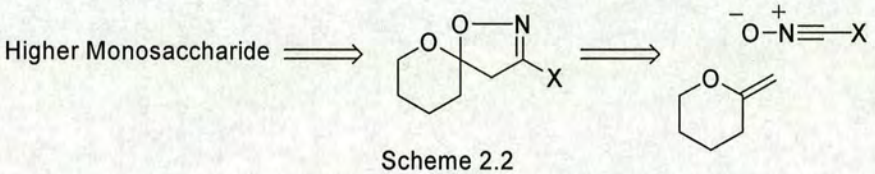
KDO, **28**

2.2 Synthetic Strategy

A number of approaches to higher monosaccharides are explored in this thesis. The first was based on previous work within the group. Young and M^{c}Ghie employed nitrile oxide cycloaddition chemistry in the synthesis of 7-deoxynonoses, 7-deoxydecoses and 6-deoxyundecoses.[1,14,16] It was hoped to develop this methodology in order to apply it to the production of deoxyheptoses and deoxyoctoses. It was proposed to carry out chain extension by the [3+2] cycloaddition of a nitrile oxide at both the non-reducing terminus of an ω-unsaturated hexofuranose (Scheme 2.1) and at the reducing terminus of a series of 1-methylene hexopyranoses and heptopyranoses (exoglycals, Scheme 2.2) resulting in 5-substituted isoxazolines, from which the higher monosaccharides could be produced by reductive ring cleavage.

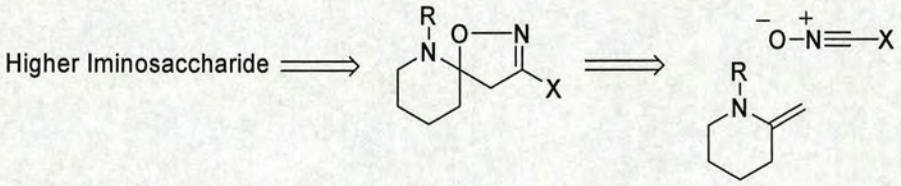


Scheme 2.1



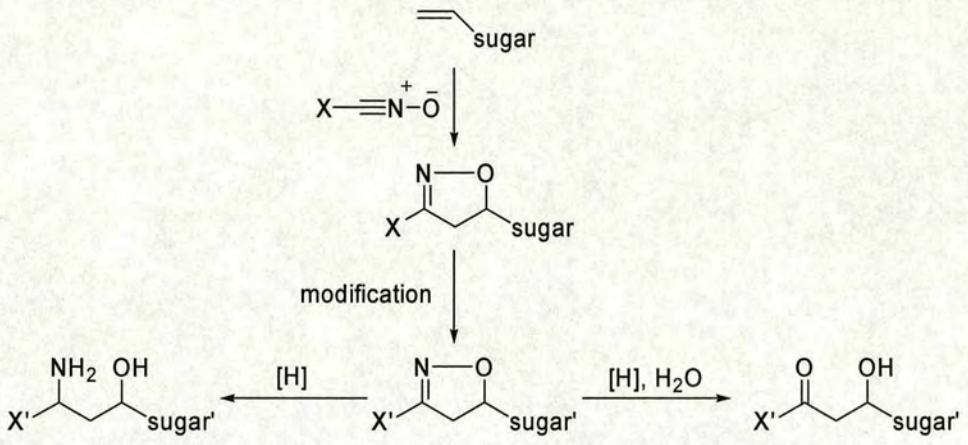
Scheme 2.2

It was also proposed to expand the work discussed above to the chain extension of sugar-based enamines using nitrile oxide cycloaddition chemistry to give higher iminosugars (Scheme 2.3).



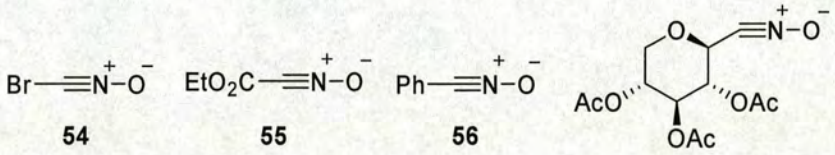
Scheme 2.3

Isoxazolines are stable to a variety of conditions allowing for the modification of the groups in the 3- and 5-positions without interference to the ring. This will allow access to an increased variety of isoxazolines. Reductive cleavage of the ring can yield a variety of functionalities, including β-hydroxy ketones and γ-amino alcohols (Scheme 2.4).[3,4]



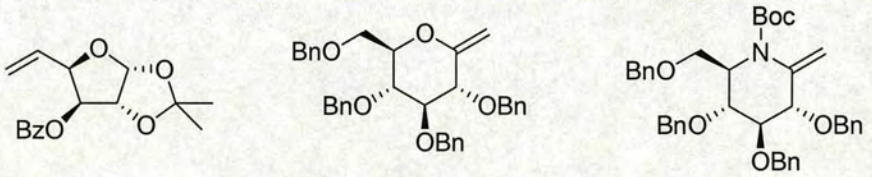
Scheme 2.4

The nitrile oxides chosen for study were bromonitrile oxide (**54**), carbethoxyformonitrile oxide (**55**), benzonitrile oxide (**56**) and a xylose-derived nitrile oxide (**57**). These were generated either by dehydrohalogenation of the corresponding halogenated oximes or dehydration of the nitromethylxylose.

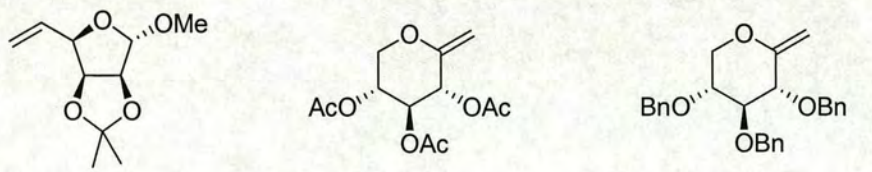


54 **55** **56** **57**

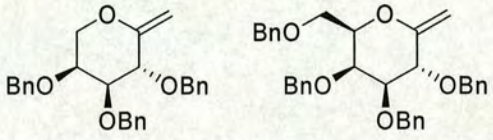
The dipolarophiles used were based on a series of sugars; **58**, **59** and **60** were derived from D-glucose, **61** was prepared from D-mannose, **62** and **63** were synthesised from D-xylose, while **64** and **65** were based on L-arabinose and D-galactose, respectively. These were prepared using a variety of methods that will be discussed in greater detail later.



58 **59** **60**

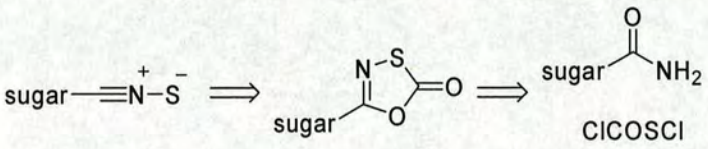


61 **62** **63**



64 **65**

The final area of work is the synthesis of a number of sulphur-containing *C*-glycosides. This area stems from past work within the group using alkyl and aryl oxathiazolones as precursors for the 1,3-dipolar cycloaddition of nitrile sulfides to various of dipolarophiles.

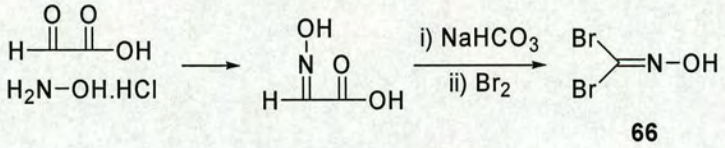


Scheme 2.5

In the synthesis of the nitrile sulfide-based *C*-glycosides it was hoped to take chemistry previously used in the group for alkyl and aryl nitrile sulfides and apply it to saccharides. It was intended to prepare these compounds by trapping pyranosyl nitrile sulfides, eg with ethyl cyanoformate or dimethyl acetylenedicarboxylate. It was proposed to generate the nitrile sulfides by thermal decarboxylation of 5-pyranosyl-1,3,4-oxathiazol-2-ones, and to prepare the latter by treatment of the corresponding carboxamide with chlorocarbonylsulfenyl chloride (Scheme 2.5). The nitrile sulfides used were based on two sugars, D-xylose and D-glucose.

2.3 Synthesis of Nitrile Oxide Precursors

2.3.1 Synthesis of Dibromoformaldoxime (66)

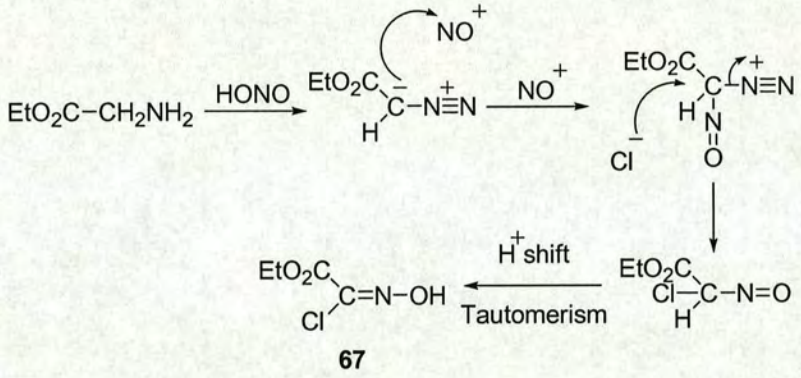


Scheme 2.6

Dibromoformaldoxime was prepared using the method of Vyas *et al*,[71] as described by Boyd (Scheme 2.6).[72] Treatment of aqueous glyoxylic acid with hydroxylamine hydrochloride followed by addition of sodium bicarbonate and bromine afforded the product as a solid that

was recrystallised from hexane to leave white crystals (29%, overall). It was subsequently found that this compound decomposes within two months of production, resulting in the reduced yields of subsequent reactions. It was therefore prepared shortly before use.

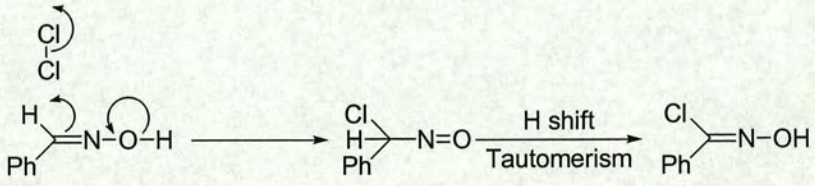
2.3.2 Synthesis of Ethyl Chlorooximidoacetate (67)



Scheme 2.7

This compound was produced employing the approach of Skinner,[73] by reacting glycine ethyl ester hydrochloride with hydrochloric acid and sodium nitrite while ensuring that the temperature of the reaction did not exceed –20°C. The product was isolated as a white crystalline solid (39%). The proposed mechanism for the reaction is shown in Scheme 2.7.

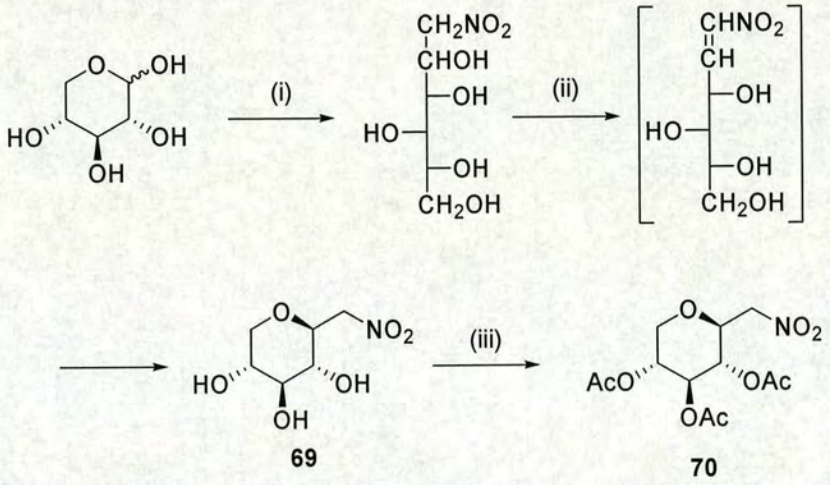
2.3.3 Synthesis of Benzohydroximoyl Chloride (68)



Scheme 2.8

The title compound was produced using the method of Chiang,[74] which involved chlorine being bubbled through a solution of α-benzaldoxime in DCM at –10°C. This resulted in a yellow solution, which yielded a white solid that was recrystallised from pentane (69%). The suggested mechanism for the reaction is shown in Scheme 2.8.

2.3.4 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-nitro-D-*gulo*-heptitol (3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane) (70)



(i) NaOMe, CH_3NO_2, MeOH; (ii) H_2O, reflux; (iii) Ac_2O, TfOH

Scheme 2.9

The first stage of the synthesis of the title compound was to add nitromethane to the sugar at the anomeric position employing the Fischer-Sowden reaction.[75] The product was then heated to achieve dehydration and ring closure to form **69**. Protection of the hydroxyl groups was achieved with acetic anhydride to give 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**70**) as a white crystalline solid (37% from D-xylose) (Scheme 2.9). The ^{1}H NMR spectrum showed that the β-anomer had been formed. The observed coupling between 2-H and 3-H was 10.1 Hz, which is consistent with a trans-diaxial arrangement for these protons. If the α-anomer had been produced then the axial-equatorial arrangement of these protons would be expected to give $J_{2,3}$ ~3 Hz. Of the four possible structures (Figure 2.1) the β $^5C_2$ form is favoured, as this is the arrangement where all the substituents are in the more stable equatorial positions.

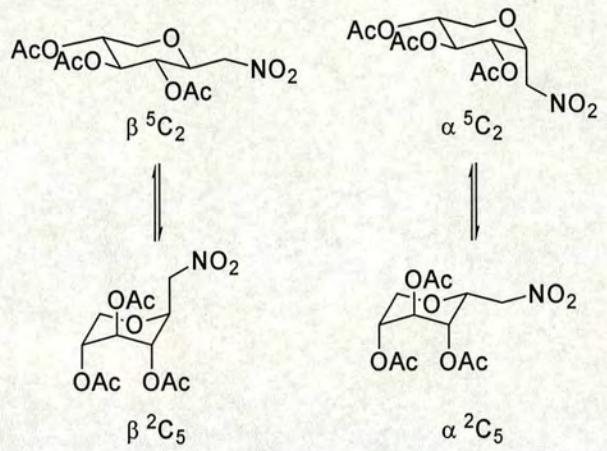
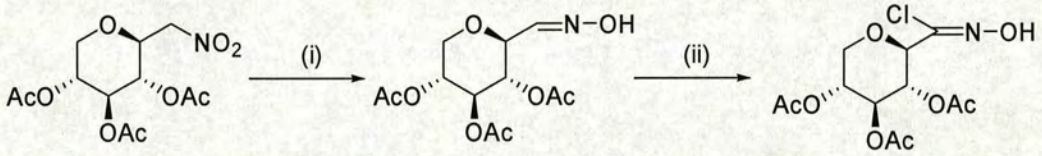


Figure 2.1

2.3.5 Synthesis of 2,6-Anyhydro-3,4,5-tri-*O*-acetyl-1-chloro-1-deoxy-1-hydroxyimino-D-*glycero*-β-D-*xylo*-hexitol (72)



70 **71** **72**

i) $SnCl_4$, NEt_3, HSPh, THF; i) Cl_2, $CHCl_3$

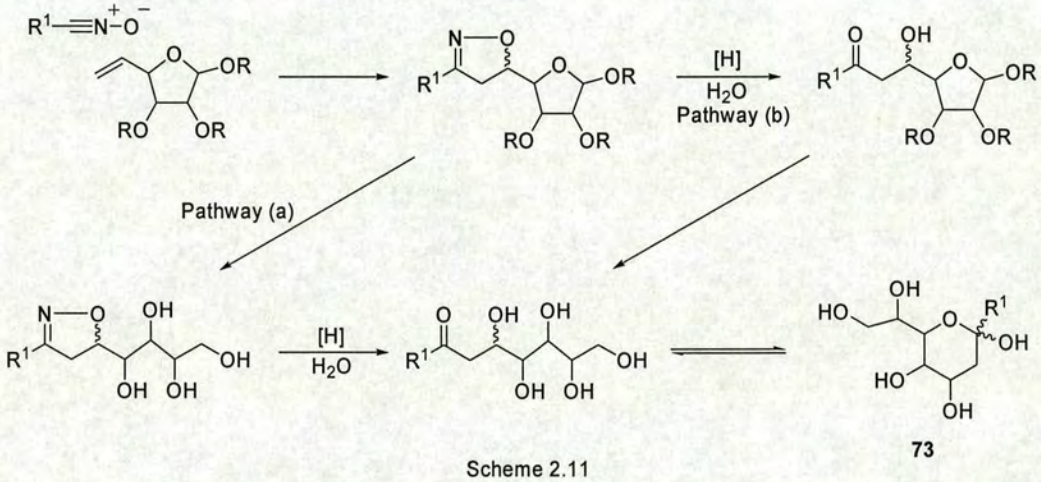
Scheme 2.10

The title compound was prepared in a two step process (Scheme 2.10) from the acetylated nitromethyl xylose **70** via the pyranosyl oxime **71**. The first step followed the method of Baker *et al*,[76] which used the reduction procedure developed by Bartra *et al*.[77] The protected nitromethyl xylose was reacted with tin(IV) chloride, triethylamine and thiophenol to give the xylose oxime as an oil in a 65% yield. The oxime was then converted quantitatively to the hydroximoyl chloride **72** by chlorination using the same method as that employed for the benzohydroximoyl chloride (Section 2.3.3).[74]

2.4 Synthesis of Hex-5-enofuranosides

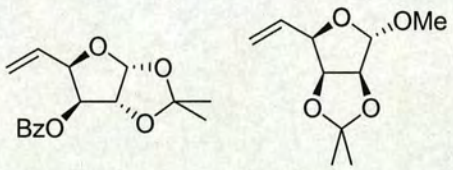
2.4.1 Synthetic Targets

The targets for this work were a series of ulosonic acid analogues and it was hoped that the application of nitrile oxide/isoxazoline chemistry to sugar dipolarophiles would allow access to such derivatives. There are two potential pathways to these higher monosaccharide analogues **73** (Scheme 2.11). In pathway (a) the sugar ring will be deprotected prior to hydrolytic ring cleavage of the isoxazoline, while in route (b) the isoxazoline ring opening will occur first. The two sugar alkenes selected for initial study were based on D-glucose **58** and D-mannose **61**. The synthesis of these alkenes is discussed below.



Scheme 2.11

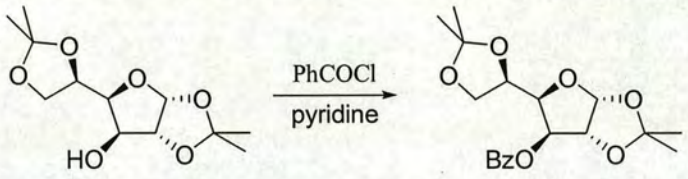
73



58 **61**

2.4.2 Synthesis of 3-*O*-Benzoyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-*xylo*-hex-5-enofuranose (58)

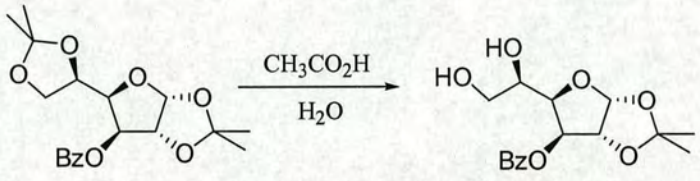
This alkene was synthesised in four steps from diacetone-D-glucose (1,2:5,6-di-*O*-isopropylidene-D-glucose, **74**).[78] In the first step (Scheme 2.12) the free hydroxyl group in the 3-position was converted into the benzoate ester **75** by treatment with benzoyl chloride in pyridine. The crude product was taken on to the next stage without purification.



74 **75**

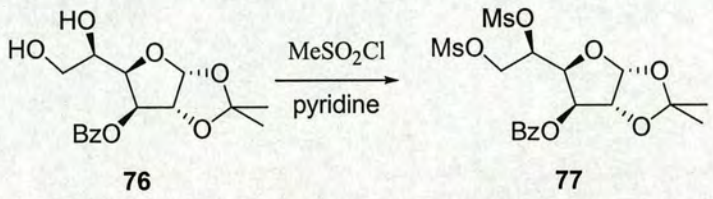
Scheme 2.12

The second step required the selective removal of the isopropylidene group in the 5,6-positions while leaving intact the other acetal at the 1,2-positions (Scheme 2.13). This was achieved by mild acid hydrolysis. The difference in reactivity between the two sites can be attributed to the steric hindrance afforded by the fused ring system that limits attack at the 1,2-positions.[78] The hydrolysis was carried out using glacial acetic acid in water (40°C) and afforded the crude product **76** as a brown oil, which was taken on to the next step without further purification.



75 Scheme 2.13 **76**

In the third stage (Scheme 2.14) the 5,6-diol was reacted with methanesulphonyl chloride in pyridine. The resulting dimesylate **77** was recrystallised from ethanol to give white crystals (28% overall from diacetone-D-glucose, **74**). The structure of the product was confirmed by comparison of the ^{1}H NMR data with previous work in the group.[79]

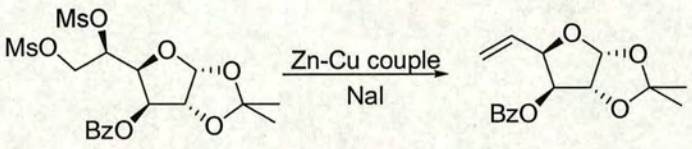


76 **77**

Scheme 2.14

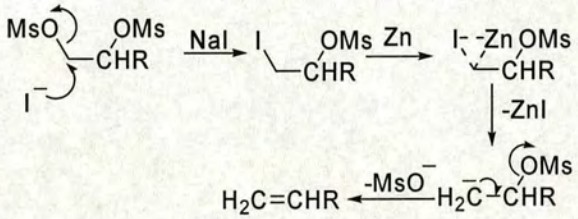
The final step (Scheme 2.15) required the elimination of the two mesylate groups at the 5- and 6-positions of compound **77** to give the desired alkene **58**. This was achieved using a modified Tipson-Cohen procedure[80] involving reaction of the dimesylate with a freshly prepared Zn/Cu couple in the presence of sodium iodide in DMF. The mechanism proposed

for this reaction is shown in Scheme 2.16.[80] The product was isolated as a crystalline solid in 77% yield (22% from diacetone D-glucose) and was identified by its melting point and using ^{1}H and ^{13}C NMR spectroscopy.



77 **58**

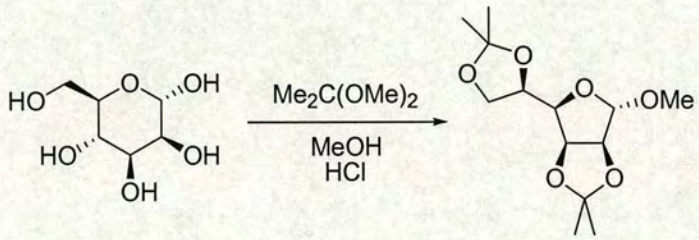
Scheme 2.15



Scheme 2.16

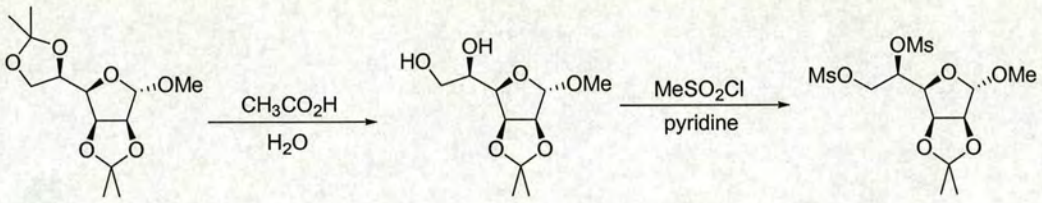
2.4.3 Synthesis of Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (61)

This alkene was produced in a four step process from D-mannose as previously reported.[81] The first step required the protection of the sugar in the furanose form **78** (Scheme 2.17) which was achieved by heating the starting material in the presence of 2,2-dimethoxypropane, methanol and conc. HCl. The crude product was taken on to the next stage without further purification.



Scheme 2.17 **78**

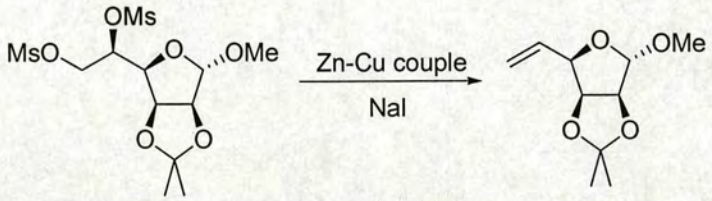
In the second step the isopropylidene group at the 5,6-position (Scheme 2.18) was selectively removed by mild acid hydrolysis. The hydrolysis was carried out using glacial acetic acid in water and afforded the crude product **79** as a brown oil, which was taken on to the next step without further purification. The 5,6-diol was then reacted with methanesulphonyl chloride in pyridine to give the dimesylate **80** (Scheme 2.18) that was recrystallised from ethanol to yield white crystals (31% overall from D-mannose). The product was identified by its melting point and ^{1}H NMR data by comparison with the previous work in the group.[79]



78 **79** **80**

Scheme 2.18

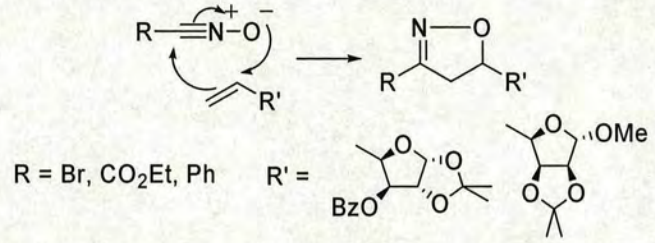
The Tipson-Cohen procedure described above for **58** was also used to convert dimesylate **80** into the target alkene **61**. This gave the desired product (Scheme 2.19) as an oil that solidified when left overnight in a freezer (77%, 23% from D-mannose). The title compound was identified by comparing the ^{1}H and ^{13}C NMR spectra with the literature.[82]



80 **61**

Scheme 2.19

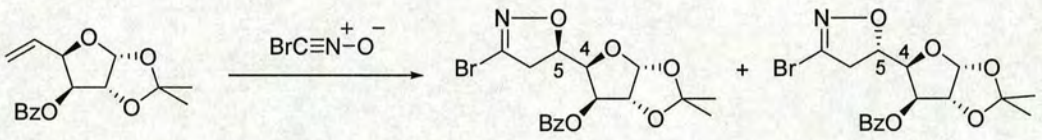
2.5 Nitrile Oxide Cycloadditions to Hex-5-enofuranosides



Scheme 2.20

The cycloaddition reactions were all carried out under the conditions developed by Huisgen,[12,13] which involves the *in situ* generation of the nitrile oxide by dehydrohalogenation of the corresponding hydroximoyl halide in the presence of the alkene (1:1.2). The generation of the nitrile oxide is controlled by slow addition of triethylamine to the reaction mixture over several days (by syringe pump), thus inhibiting furoxan formation. A further step that can be employed to limit furoxan formation is to ensure that the alkene is present in a large excess relative to the nitrile oxide (Scheme 2.20).

2.5.1 Synthesis of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-bromo-2-isoxazoline (81)



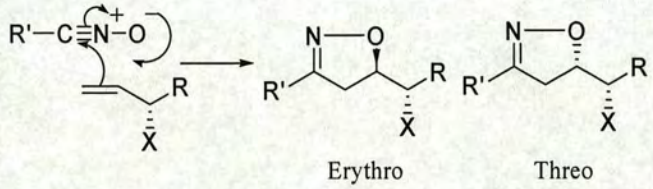
58 **81a** Erythro **81b** Threo

Scheme 2.21

The cycloaddition reaction was carried out as described above (Scheme 2.21). The dibromoformaldoxime and the alkene **58** were dissolved in sodium-dried ether to which triethylamine in ether was added over three days. On completion of base addition the mixture was left to stir overnight. The work up gave an oil that contained the isoxazoline cycloadduct, which was present as a mixture of diastereomers, together with some unreacted alkene. The presence of the disastereomers were shown by a figure-of-eight arrangement of

product spots on the tlc plate and this was confirmed by the ^{1}H (Appendix 4a) and ^{13}C NMR spectra which showed two sets of peaks attributable to the isoxazoline rings.

The crude mixture was subjected to dry flash chromatography and yielded, in order of elution, the unreacted alkene (58%) and a mixture of the two isoxazoline diastereomers **81a** and **81b** in 67% yield (based on consumed alkene). The isomer ratio was determined to be 87:13 by comparison of their ^{1}H NMR spectra. In the proton NMR the most suitable protons for determining this were those at the anomeric position as they had the greatest chemical shift of the sugar protons; the signals for the two isomers are also well separated ($\Delta\delta_H = 0.08$ ppm) and not obscured by any other signals.



Erythro Threo

Scheme 2.22

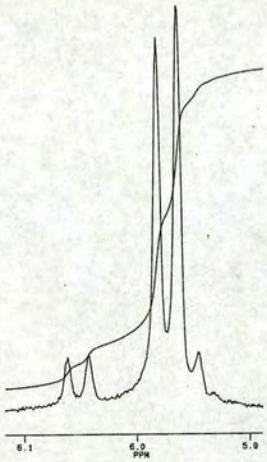


Figure 2.2: ^{1}H NMR of the anomeric proton

The two diastereomers could not be separated by dry flash chromatography and the major isomer **81a** (30%) was therefore isolated by recrystallisation from ethanol. Products **81a** and **81b** were assigned as having erythro and threo relationships (Scheme 2.22), respectively. This designation is based on the relative stereochemistry at C-4 and C-5. The major isomer was assigned 5*R*4*S* stereochemistry by correlation with examples of sugar isoxazolines with

eleven carbons in the backbone as reported in the literature,[1] which showed that the major 5*R*4*S* isomer (erythro) had the lower chemical shift for the anomeric H atom than the 5*S*4*S* minor isomer (threo) (Table 2.1, Figure 2.2).[14] The cycloadduct **81a** was characterised by ^{1}H and ^{13}C NMR spectroscopy, and the mass was confirmed using FAB mass spectroscopy.

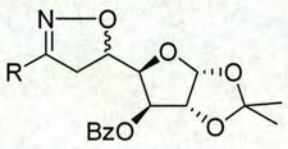
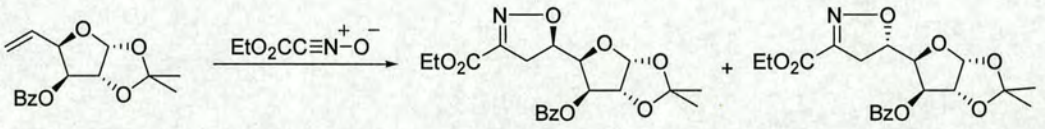


Table 2.1: Chemical Shifts of Cycloadduct Diastereomers (^{1}H NMR)

cycloadduct	major δ_H 1-H/ppm	minor δ_H 1-H/ppm	R
81	5.97	6.05	Br
82	5.96	6.02	CO_2Et
83	5.99	6.09	Ph

2.5.2 Synthesis of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (82)



58 **82a** **82b**

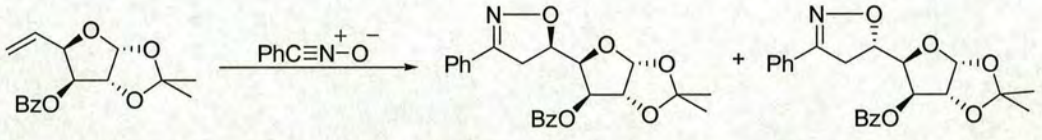
Scheme 2.23

The cycloaddition to give the title compound was carried out in the same manner as the previous reaction with the nitrile oxide being generated *in situ* by the slow addition of the base to the reaction mixture containing alkene **58** and ethyl chlorooximidoacetate (Scheme 2.23). From the reaction mixture was isolated an oil that contained unreacted alkene and the desired cycloadduct **82** as a mixture of diastereomers.

The oil was then subjected to dry flash chromatography to give, in order of elution, the unreacted alkene (41%), followed by a mixture of the isoxazoline diastereomers (67%, based

on consumed alkene). The isomer ratio was found to be 87:13 from the proton NMR spectrum (Appendix 4b). The isomers of this particular cycloadduct were not separable by chromatography and as a result the major (5*R*) adduct **82a** (Table 2.1) was isolated by recrystallisation of the crude product from ethanol to give white crystals. The cycloadduct was characterised by its ^{1}H and ^{13}C NMR spectra and the mass was confirmed using FAB mass spectrometry.

2.5.3 Synthesis of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-phenyl-2-isoxazoline (83)



58 **83a** **83b**

Scheme 2.24

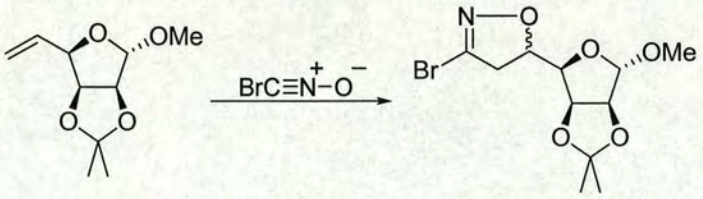
The cycloaddition was carried out by the standard method already described (Scheme 2.24). However, the base was added to the reaction mixture containing benzohydroximoyl chloride and alkene **58** over two days rather than over three days. The reaction produced an oil that contained the unreacted alkene and a mixture of the two isoxazoline diastereomers.

Dry flash chromatography of the crude product afforded the unreacted alkene (22%) and the two product diastereomers **83** (69%, based on consumed alkene), the isomer ratio of which was determined to be 83:16 from the proton NMR spectrum of the product mixture (Appendix 4c). As with the two cases above, the diastereomers could not be separated by column chromatography, but the major (5*R*) isomer **83a** (Table 2.1) was isolated by recrystallisation from ethanol. This compound was characterised by its melting point, ^{1}H and ^{13}C NMR and the mass was confirmed using FAB mass spectrometry.

2.5.4 Synthesis of 3-Bromo-5-(1-*O*-methyl-2,3-*O*-isopropylidene-α-D-*lyxo*-furanos-4-yl)-2-isoxazoline (84)

This reaction was carried out in an identical manner (Scheme 2.25) to the previous cycloadditions by addition of triethylamine in ether to a mixture of alkene **61** and

dibromoformaldoxime in sodium-dried ether. This resulted in the production of an oil containing unreacted alkene as well as the two isoxazoline diastereomers.



61 **84**

Scheme 2.25

The unreacted alkene (79%) was removed using dry flash chromatography to leave the inseparable diastereomers (92%, based on consumed alkene) as an oil. The compound was characterised from proton and carbon NMR and the isomer ratio was determined to be 79:21 from the ^{1}H NMR spectrum (Appendix 4d). It was not possible to isolate the major isomer by crystallisation from the crude mixture of isoxazolines.

2.5.5 Selectivity of Nitrile Oxide Cycloaddition Reactions

Nitrile oxide cycloadditions to cyclic chiral allyl ethers results in π-facial selectivity; this is due to the faces of the alkene not being identical causing a degree of diastereoselectivity in the reactions. The selectivity is affected by electronic and steric factors imparted by the alkene substituents.[4] The π-facial selectivity may be explained by the "inside-alkoxy" effect. This proposal by Houk *et al*[83] examines the transition state of the reaction between 1,3-dipoles and cyclic and acyclic chiral allyl ethers and chiral allyl alcohols by considering the relative positions of the substituents in the transition state.

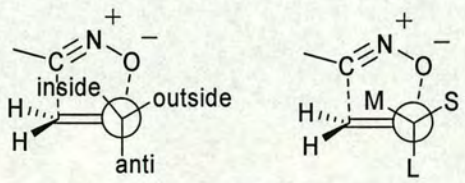


Figure 2.3

As can be seen from Figure 2.3 there are three possible positions for the substituents to take up in the transition state of the reaction between a nitrile oxide and a monosubstituted alkene.[79] The inside position is generally favoured by the medium sized substituents, the

outside position is preferred by the smallest group and, finally, the largest group favours the anti position.[4] Looking, more specifically, at chiral cyclic allylic ethers there are six possible staggered transition structures for the cycloaddition of a nitrile oxide to a chiral allyl ether (Figure 2.4). Theoretical calculations by Houk *et al*[83] of the relative energies of the transition states places them in ascending order of energy A<A'<B<B'<C'<C. The major erythro adduct results from transition states A, B and C and the minor threo adduct results from A', B' and C'.[83]

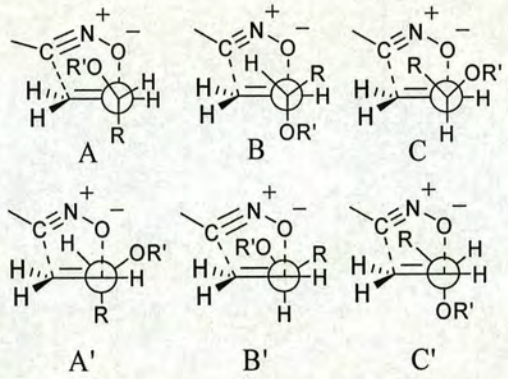
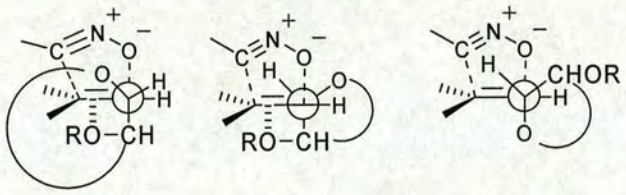


Figure 2.4

There are several reasons for the selectivity of these reactions. The alkoxy group prefers the inside-position as this allows the slight rotation of the alkoxy and alkyl groups to a more relaxed conformation, this would not be possible in the outside-position due to the interaction between the lone pairs of the alkoxy oxygen and those of the nitrile oxide oxygen. The alkoxy group also shuns the anti-position as this would have a destabilising effect on the transition state because of the electron withdrawal from an already electron deficient transition state. This electron withdrawal is attributed to secondary bonding interactions where the σ*-orbital of the carbon-oxygen bond interacts with the π-orbital of the alkene. This overlap is at its maximum when the alkoxy group takes up the anti-position and at a minimum when the group adopts the inside-position. The alkyl group prefers the anti-position as this stabilises the transition state through electron donation from the σ-orbital of the carbon-carbon bond to the overlapping π-orbital of the alkene. The two other positions are unfavoured due to the lack of rotation that would be achievable by the group in either position to more relaxed conformation. The hydrogen takes up the outside position by default to allow the alkoxy and alkyl groups to satisfy their electronic and steric requirements.[84,85]

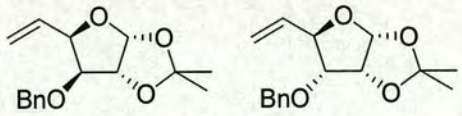
The difference in selectivity observed for the major and minor diastereomers of isoxazoline **84** (79:21) versus isoxazolines **81**, **82** and **83** (87-84:13-16) may be explained by the experimental error rather than by the "inside-alkoxy" effect. They can also be rationalised by the conclusions of De Micheli and co-workers.[78] They reported that for some nitrile oxide cycloadditions to D-*xylo*-hex-5-enofuranosides the erythro:threo ratio was larger than could be rationalised by Houk's "inside-alkoxy" effect. They concluded that some other interaction must have been affecting the stability of the transition states. It was surmised that the homoallylic oxygen in the 3-position was important in destabilising A and A' (Figure 2.5). The lone pair of this oxygen may exert a through space interaction in these transition states withdrawing electron-density from the system. However, in the next lowest energy transition state, B, the homoallylic oxygen is orientated in such a way that it cannot destabilise the double bond (Figure 2.5). B affords the erythro diastereomer thus explaining the increased levels of this product over the threo.



A A' B

Figure 2.5

This interaction has been further demonstrated by previous work in the group,[86] where the configuration of the 3-position was inverted to explore the difference in diastereoselectivity of the cycloaddition reaction. It was found that the reaction between benzonitrile oxide and 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**85**) was found to be highly stereoselective (73-93% d.e.), while the cycloaddition of benzonitrile oxide to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (**86**) gave a considerably lower selectivity (16% d.e.). These findings support De Micheli's conclusions and add further weight to the "inside-alkoxy" effect rationalisation.



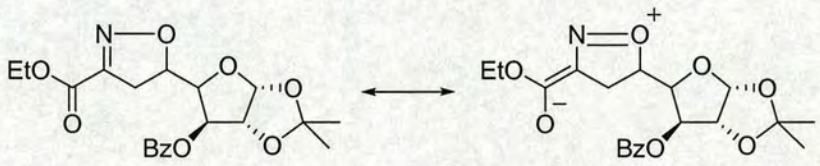
85 **86**

This may explain (Figure 2.5) the lower selectivity observed for isoxazoline **84** as the importance of transition state B is dependent upon the ability of the group in the 3-position to rotate to the most stable configuration, in the case of this isoxazoline the oxygen is locked in position as a 2,3-*O*-isopropylidine group. This results in transition state B being of limited importance in this cycloaddition, therefore less of the erythro product was generated. While the transition states that yield isoxazolines **81**, **82** and **83** are all capable of allowing rotation at this position, consequently B is again an important transition state for generating the erythro product in the cycloaddition process.

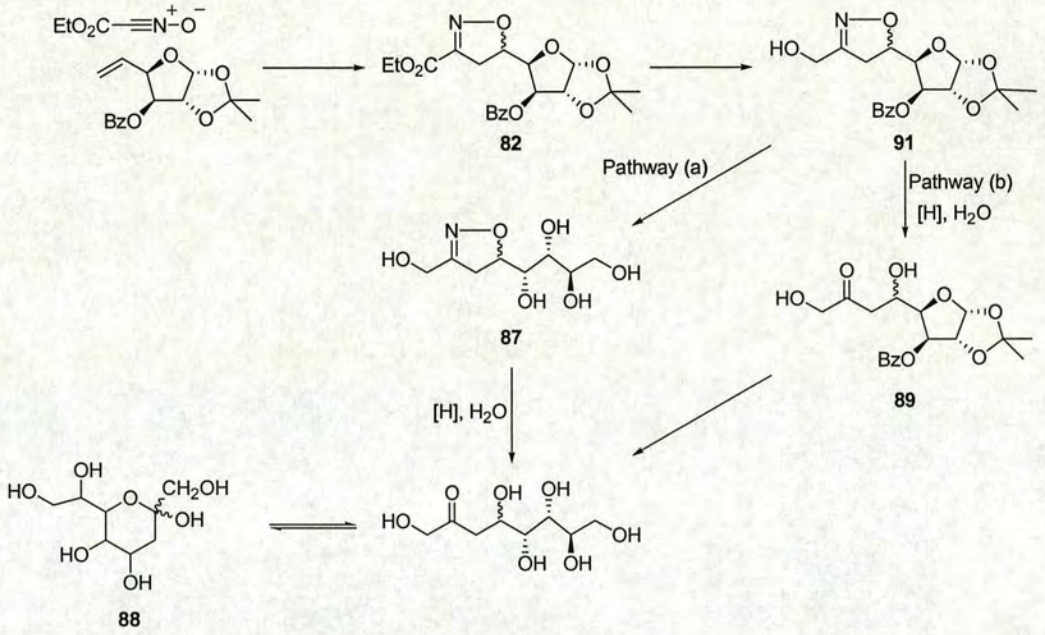
2.6 Reactions of Cycloadducts

2.6.1 Reduction of the Ester Groups of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (82)

Previous work in the group found that ring cleavage of 3-carbethoxy-2-isoxazolines was slow. This was a attributed to interaction, by resonance, of the carbonyl of the ester with the isoxazoline ring (Scheme 2.26),[87] as a result the isoxazoline ring is not readily cleaved. The carbethoxy group was therefore to be converted to the alcohol prior to ring opening. It was hoped that this would provide a route to ulosonic acid analogues. Scheme 2.27 illustrates two potential routes to ulosonic acid analogues using this approach, for pathway (a) the sugar ring is deprotected and the resulting aldehyde is reduced to the alcohol to afford isoxazoline **87**. The isoxazoline will then be hydrolytically cleaved to yield the ulosonic acid analogue **88**. In pathway (b) the opposite method is taken whereby the isoxazoline will be cleaved to give β-hydroxyketone **89** which will then be deprotected to give the ulosonic acid analogue **88**.

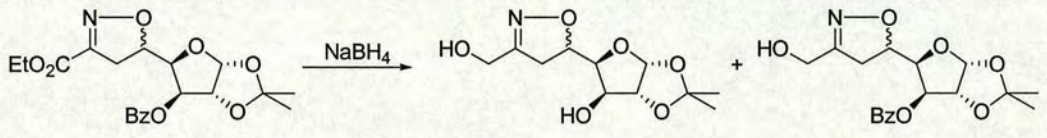


Scheme 2.26



Scheme 2.27

The approach employed for the reduction of the ester group at the 3-position of the isoxazoline ring used sodium borohydride (4 eq.) as the reducing agent. This was dissolved in dry ethanol and slowly added to a stirred solution of isoxazoline **82** in dry ethanol at room temperature. On consumption of the starting material the reaction mixture afforded an apparently pure (tlc) white solid in low yield, after purification by dry flash chromatography. Examination of the product by proton NMR spectroscopy (Appendix 4e), however, indicated the presence of two compounds in a ca. 1:1 ratio. On the basis of the NMR spectrum the two compounds were assigned structures **90** (11%) and **91** (8%). There were signals for two OH groups and an aromatic group; this suggests that there is one compound where the isoxazoline ester has been reduced to the alcohol and has also been deprotected at the 3-position by the removal of the benzoate to leave a second alcohol group (**90**). The isoxazoline ester of the second compound has been reduced to the alcohol but the benzoate has been left intact (**91**) (Scheme 2.28). Therefore, it was decided to alter the conditions to completely remove the benzoyl group in the 3-position in an effort to produce, solely, isoxazoline **90**.



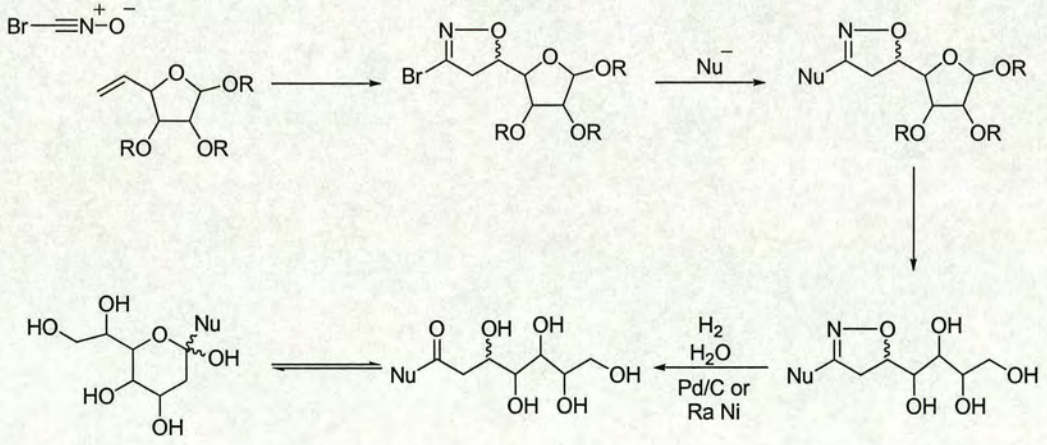
82 **90** **91**

Scheme 2.28

In an effort to obtain only alcohol **90** it was decided to increase the quantity of sodium borohydride to 20 eq.[88] As before, tlc indicated that the starting material had been consumed and a single compound had been produced. However, proton NMR (Appendix 4f) and the mass spectrum showed the white solid to be a mixture of **90** and **91**. This experiment afforded deprotected alcohol **90** as the major product in a ca. 13:1 ratio with alcohol **91**. This method had a much-improved yield, however, a mixture of alcohols was still obtained and it was not possible to separate the two alcohols or to isolate either as single diastereomers.

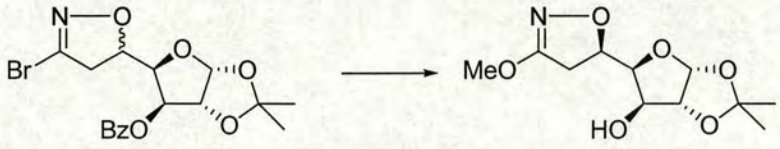
2.6.2 Substitution Reactions

In order to increase the range of available isoxazolines it was intended to substitute the bromine atom in the 3-position of isoxazolines **81** and **84** with a series of nucleophiles. This would allow access to a number of substituted isoxazolines using one common nitrile oxide precursor. Furthermore, this approach would afford isoxazolines for which there is no reasonable precursor readily available. To test the basis of this chemistry it was decided to carry out model reactions using methoxide as the nucleophile employing a modified approach from Nishi *et al.*[89] It was hoped that this would allow easy access to an array of ulosonic acid analogues (Scheme 2.29).



Scheme 2.29

2.6.2.1 Synthesis of 5-(1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-methoxy-2-isoxazoline (92)



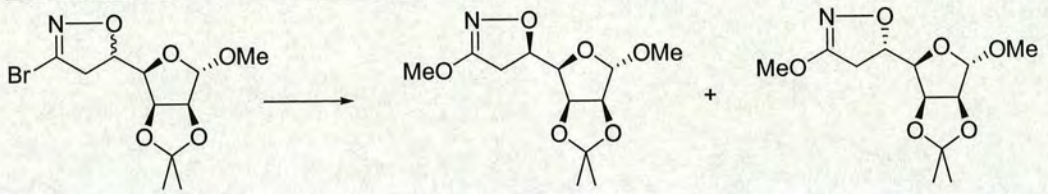
81 **92**

Scheme 2.30

A solution of the 3-bromoisoxazoline **81** (*R*:*S* 87:13) in a lithium methoxide/methanol solution was heated at reflux until no starting material remained (tlc) and from the reaction mixture was isolated an oil in 66% yield (Scheme 2.30). The product was identified as the title compound and assigned as being the 5*R*-isomer by comparison with the proton NMR spectrum of the starting material; the former had peaks at 3.88 ppm and 3.05 ppm that corresponded to the 3-methoxy group and a hydroxyl group respectively. In contrast to the starting material, which was a mixture of isomers **81a** and **81b**, the product proved to be a single isomer. None of the minor isomer was isolated.

2.6.2.2 Synthesis of 3-Methoxy-5-(methyl-2,3-*O*-isopropylidene-α-D-*lyxo*-furanosyl-4-yl)-2-isoxazoline (93)

Cycloadduct **86** (*R*:*S* 79:21) was refluxed in lithium methoxide/methanol solution, until no starting material remained (tlc), to give the substitution product as a mixture of isomers in a 78% yield (Scheme 2.31). The isomeric products were separated by column chromatography. This gave the major 5R-isomer **93a** as an oil (63% isolated yield) and the minor 5S-isomer **93b** as an oil (15% isolated yield). The evidence for the incidence of both cycloadducts was found in the proton NMR spectra of the starting material and the products. The former showed one singlet at 3.30 ppm corresponding to the 1-methoxy group attached to the sugar ring, while both product spectra contained peaks attributable to the 1-methoxy group and the 3-methoxy group of the isoxazoline ring at 3.88 ppm and 3.35 ppm, respectively, for the major isomer, and 3.84 ppm and 3.33 ppm for the minor isomer.



84 **93a** **93b**

Scheme 2.31

These reactions indicate that cycloadducts **81** and **84** easily undergo nucleophilic substitution reactions and suggest that a number of substituted isoxazolines should be easily accessible via this route. This is of particular value for products where the nitrile oxide precursors may not be readily available, eg $RO-C\equiv N^{+}-O^{-}$. However, further work will be required to determine what substitution reactions are possible.

2.6.3 Ring Opening Reactions

2.6.3.1 Attempted Ring Opening of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-carbethoxy-2-isoxazoline (82)

As previous work with 3-carbethoxy isoxazolines had shown that they were slow to cleave with catalysts such as Raney Ni and Pd/C it was decided to use $Mo(CO)_6$ as the catalyst. This reaction used a method previously reported by Baraldi *et al.*[90] Isoxazoline **82** was dissolved in acetonitrile in the presence of $Mo(CO)_6$ and the resulting mixture was refluxed for 1 h. On work up no ring opening products were observed either by the tlc or in ^{1}H NMR spectrum and the starting material was recovered quantitatively.

The failure of this reaction was attributed to the stabilising effect of the carbonyl in the ester group resonating with the imine group of the isoxazoline (Scheme 2.27).

2.6.3.2 Attempted Ring Opening of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-phenyl-2-isoxazoline (83)

Isoxazoline **83** was stirred in a solution of methanol and water under a hydrogen atmosphere in the presence of Raney nickel[17] for 48 h after which time tlc showed that most of the starting material had been consumed. The reaction mixture was subjected to column

chromatography; this resulted in a low yielding unidentifiable product and recovered starting material (6%).

2.7 Conclusions

It has been shown that isoxazolines may be produced by the 1,3-dipolar cycloaddition of bromoformonitrile oxide, ethoxycarbonylnitrile oxide and benzonitrile oxide with sugar-derived alkenes. The reactions of the three chosen nitrile oxides with 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**58**) gave isoxazolines in similar yields (67-69%). π-Facial selectivity for the newly formed stereocentre at the 5-position, with isomer ratios in the range of 87-84:13-16 (*R*:*S*). It was not possible to separate the diastereomers by column chromatography. However, small quantities of the major *R*-isomer were isolated by recrystallisation.

The final cycloaddition attempted was that of bromoformonitrile oxide and methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (**61**), which gave cycloadduct **84** in a high yield (92%), but with reduced selectivity (79:21). This cycloadduct also presents problems for separation as it was not possible to isolate the diastereomers by column chromatography and, to date, has proved difficult to recrystallise.

The reductions of the carbethoxy group in 5-(3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (**82**) gave an inseparable mixture of alcohols. The substitution reactions carried out on 5-(3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-bromo-2-isoxazoline (**81**) and 3-bromo-5-(methyl-1,2-*O*-isopropylidene-α-D-*lyxo*-furanosyl-4-yl)-2-isoxazoline (**84**) were more successful. The former gave the (5*R*) 5-(1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-methoxy-2-isoxazoline (**92**) in 66% yield, while the latter gave 3-methoxy-5-(methyl-1,2-*O*-isopropylidene-α-D-*lyxo*-furanosyl-4-yl)-2-isoxazoline (**93**) as an inseparable mixture of the *R* and *S* isomers 64% and 15%, respectively. These substitution reactions provide scope for the generation of diastereomerically pure novel sugar isoxazolines for which there are no easily available nitrile oxide precursors.

The ring opening reaction attempted on 5-(3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-phenyl-2-isoxazoline (**83**) resulted in a small amount of unidentifiable product and recovered isoxazoline (6%). That attempted with 5-(3-*O*-benzoyl-1,2-*O*-

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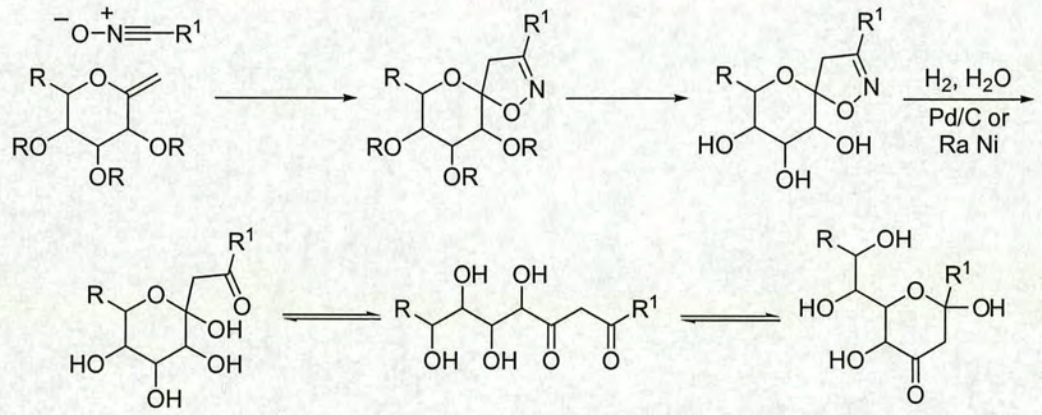
isopropylidene-α-D-*xylo*-furanosy-4-yl)-3-carbethoxy-2-isoxazoline (**82**) resulted in the quantitative return of starting material.

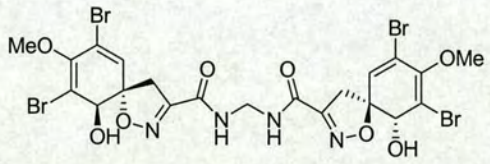
Due to the problems discussed in this section an alternative approach to higher monosaccharides was explored, based on exoglycals.

2.8 Synthesis of 1-Methylene Sugars (Exoglycals)

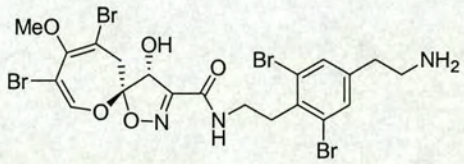
1-Methylene sugars (exoglycals) were selected as dipolarophiles as it was considered that they could provide an alternative route to ulosonic acid analogues, as illustrated in Scheme 2.32. Cycloaddition of a nitrile oxide to an exoglycal would be expected to be regiospecific affording spiroisoxazolines, which could yield ulosonic acid-like hemiketals by the ring-opening/ring-closure sequence shown below. Spiro-isoxazolines are also of biological interest in their own right. For example, bromotyrosine derived marine metabolites have been reported. Two examples of such metabolites are aerothionin (**94**) and psammaplysin-A (**95**) that contain the spirocyclohexadiene- and spiriooxepin-isoxazoline systems, respectively.[91]



Scheme 2.32



94

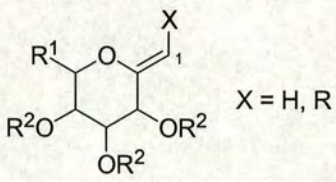


95

2.8.1 Routes to Exoglycals

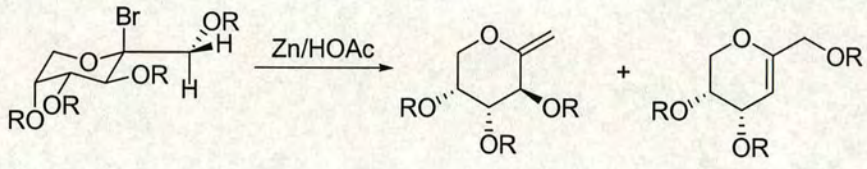
The synthesis and uses of exoglycals have been recently reviewed by Taillefumier.[92] There are two potential approaches to exoglycal synthesis, the first constructs the carbon skeleton

which undergoes an elimination reaction to give the double bond and the second method has the unsaturation included in the carbon-carbon bond formation process.[93]



96

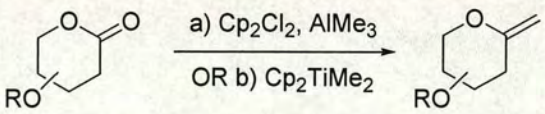
Exoglycals can be generated with or without substituents in the 1-position of **96**, the synthesis of both will be outlined. First, the production of the unsubstituted exoglycals will be discussed. The elimination of the bromide and an acyl group from a pyranosyl bromide **97**,[94] using Fischer-Zach conditions (Scheme 2.33) is one approach to the exoglycal **98**, which required treatment with copper activated zinc in acetic acid. However, the endo-glycal **99** is also produced under these conditions and, as yet, there is no method available to control the regiochemistry of this reaction.[94]



97 **98** **99**

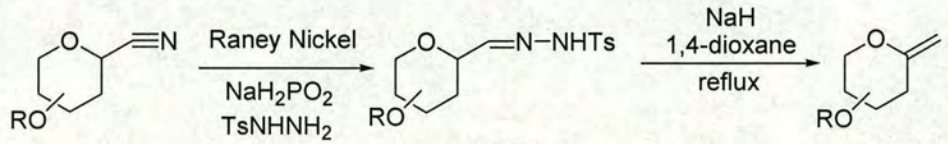
Scheme 2.33 R = Bz, Ac

Exoglycals can also be produced by the olefination of a sugar lactone (Scheme 2.34) using either the Tebbe (route a)[95] or Petasis (route b)[96] reagents. Both these approaches produce the methylidenetitanocene ($Cp_2Ti{=}CH_2$) reactive species which undergoes a [2+2] cycloaddition/cycloreversion with the carbonyl group of the saccharide to afford the methylene group.



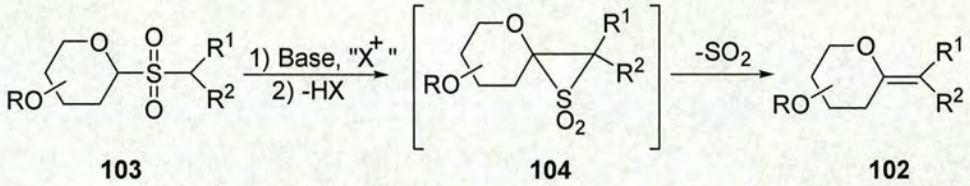
Scheme 2.34

A novel approach to exoglycals was recently reported by Tóth.[97] Pyranosyl nitriles were converted to 2,6-anhydroaldose tosyl hydrazones **100** that gave the desired exoglycal **101** when subjected to aprotic Bamford-Stevens conditions (Scheme 2.35).



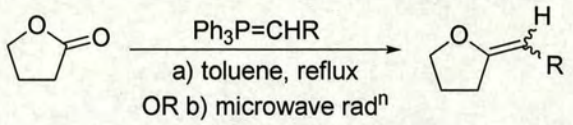
Scheme 2.35 R = Ac, Bz

The routes into 1-substituted exoglycals **102** are usually more complex than those for 1-exo-methylene sugars. The Ramberg-Bäcklund rearrangement has recently been identified as a novel route to functionalised exoglycals. This method exploits the known stability of alkyl and aryl thioglycosides, which are easily prepared and can be readily activated to give the sulphonium species.[93] In this example (Scheme 2.36) the Ramberg-Bäcklund conditions are applied to a thioglycoside *S,S*-dioxide **103** (glycosyl sulphone) to synthesise a carbon-carbon exo-double bond at the anomeric position, via the thiirane 1,1-dioxide intermediate **104**.[93]



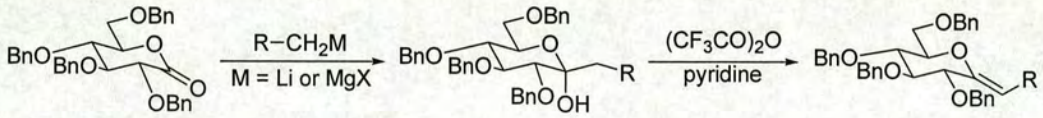
Scheme 2.36 R = Ac, Bz

Another possible route to the desired exoglycals is to employ the Wittig reaction; however only functionalised exoglycals may be produced by this route as a stabilised ylide is required.[98-100] Two possible sets of conditions (Scheme 2.37) were used to carry out this reaction, the first required the heating of the lactone and the stabilised phosphorane in toluene for 24 h at 140°C.[100] A disadvantage of this route is that the reaction must be carried out in a sealed tube. The second technique used microwave radiation to achieve reaction by placing the reactants in a microwave oven at 90°C for 1 to 2 min to give the product.[101]



Scheme 2.37 R = CO_2Me, CO_2Et, CN

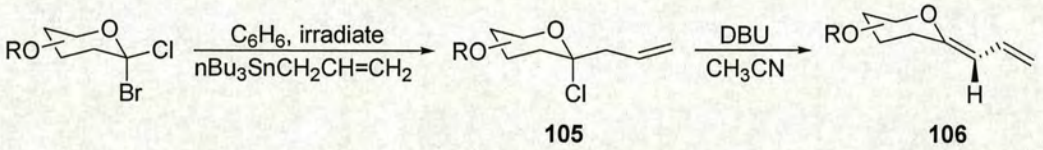
A variety of exoglycals have been produced by the addition of nucleophiles to sugar lactones to give pyranoketoses that are subsequently dehydrated using trifluoroacetic anhydride and pyridine (Scheme 2.38).[102]



R = H, C_2H_5, CO_2Et, $CH=CH_2$, $PO(OMe)_2$, SO_3Et, C_6H_5

Scheme 2.38

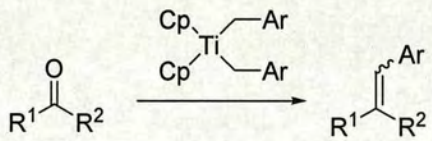
The allylation of a sugar 1,1-dihalide using two equivalents of allyltributyltin gives the allyl pyranosyl chloride **105** via a radical mechanism. This intermediate then affords the exocyclic diene **106** by a base catalysed 1,2-elimination reaction.[103] This is known as the Keck reaction (Scheme 2.39).



105 **106**

Scheme 2.39 R = Ac

A number of modified Petasis reagents have been used to produce functionalised alkenes in acyclic systems (Scheme 2.40).[104] It is possible that these may, in the future, be applied to cyclic systems and sugar lactones in particular.

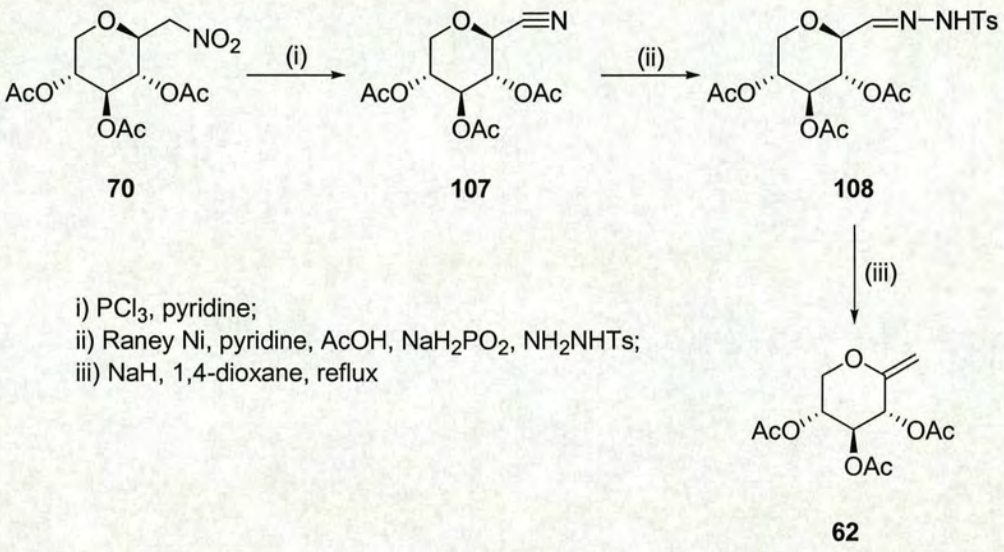


Scheme 2.40

2.9 Synthesis of Exoglycals

Two approaches were considered for the preparation of the target 1-methylene sugars: the route used by Tóth *et al*[97] proceeding via tosyl hydrazones as intermediates (Scheme 2.35), and that involving Petasis olefination of sugar lactones (Scheme 2.34).

2.9.1 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-D-*xylo*-hex-1-enitol (62)

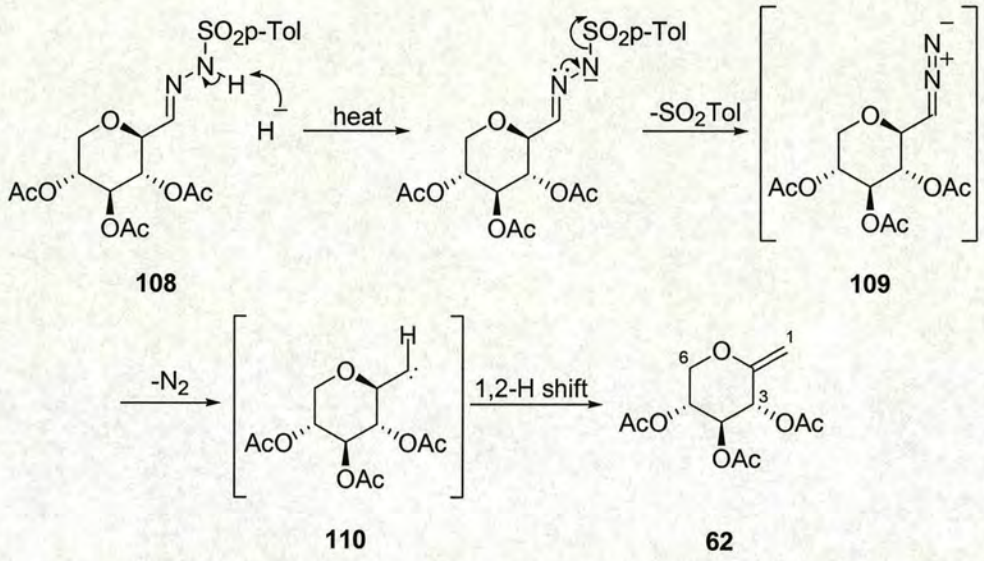


i) PCl_3, pyridine;
ii) Raney Ni, pyridine, AcOH, NaH_2PO_2, NH_2NHTs;
iii) NaH, 1,4-dioxane, reflux

Scheme 2.41

The acetylated nitromethyl xylose **70** was first converted into the nitrile **107** (84%) by treatment with phosphorous trichloride in pyridine following the method of Köll (Scheme 2.41).[105]

2,6-Anyhdro-3,4,5-tri-*O*-acetyl-β-D-xylose tosylhydrazone (**108**) was then prepared from the protected xylose nitrile, produced in the above step, utilising a method modified by Tóth *et al*[98] from those of Albrecht *et al*[106] and Dettinger *et al.*[107] Raney nickel was added to a stirred solution of pyridine, water and acetic acid, to which sodium hypophosphite, tosyl hydrazine and the xylose nitrile were added. The reaction mixture was allowed to stir until no starting material remained (tlc). The hydrazone was isolated from the reaction mixture as a white solid (86%).



Scheme 2.42

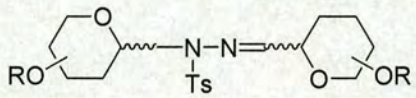
The target exoglycal **62** was produced from the xylose hydrazone **108** in a 51% yield [36% overall from 2,6-anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-nitro-D-*gulo*-heptitol (**70**)] using aprotic Bamford-Stevens conditions as employed by Tóth.[97] The hydrazone was dissolved in dry 1,4-dioxane and added dropwise to a refluxing suspension of NaH in dry 1,4-dioxane. Heating was maintained until the reaction was complete (~4 h, tlc) to give the product as a colourless oil, which was characterised by ^{1}H and ^{13}C NMR spectroscopy (Table 2.2) and mass spectrometry. The reaction was presumed to involve formation of diazo compound **109** and carbene **110** as intermediates (Scheme 2.42). Evidence for the formation of the exoglycal was observed in the NMR spectra that were compared to those of the analogous compounds produced by Tóth *et al.*[97,108] The ^{1}H NMR spectrum showed a pair of doublets of doublets at 4.71 ppm and 4.97 ppm that correspond to the exocyclic alkene protons 1a-H and 1b-H, with the expected geminal and allylic couplings to 3-H [^{3}J/Hz 1a-1b 1.5, 1a-3 0.8, 1a-3 0.5]. Furthermore, the peak attributable to 3-H exhibited one major coupling in the product rather than the triplet seen in the tosylate. This is consistent with the 3-H only being coupled to one ring proton (4-H) in the product while in the tosylate it was interacting with two protons (2-H and 4-H). In the carbon spectrum a CH_2 peak was observed at 99.4 ppm, which was assigned C-1 and the quaternary C-2 peak was at 154.0 ppm. The ^{1}H NMR spectrum also shows that the pyranose ring of the exoglycal is distorted away from the ideal chair conformation. The observed couplings of 7.7 Hz and 7.6 Hz, respectively, for H-3/H-4 and

H-4/H-5 are significantly lower than those found for the tosyl hydrazone precursor **108** (9.7 and 9.5 Hz) which are more typical of an ideal chair.

Table 2.2: NMR data for **62**

Proton	δ_H/ppm	Coupling	*J*/Hz	Carbon	δ_C/ppm
1a	4.97	1a,1b	1.5	1	99.4
1b	4.71	1a,3	0.8	2	154.0
3	5.62	1b,3	0.5	3,4,5	69.2, 69.2, 72.6
4	5.35	3,4	7.7	6	67.4
5	5.30	4,5	7.6		
6a	4.42	5,6a	4.7		
6b	3.80	5,6b	8.2		
		6a,6b	11.2		

Although the above approach was successful in the example described, it was found to be difficult to reproduce with a degree of consistency and the yields obtained were lower than those originally quoted by Tóth *et al* for similar compounds.[97] Work subsequently published by Tóth *et al*[108] also indicated that this approach was not satisfactory for all sugar hydrazones. They reported that on incomplete deprotonation of the hydrazone the carbene could insert into the nitrogen-hydrogen bond of the remaining hydrazone to give compound **111**. In view of these problems and the inability to successfully scale up the reaction it was decided to explore the alternative lactone olefination route to the 1-methylenated sugars.

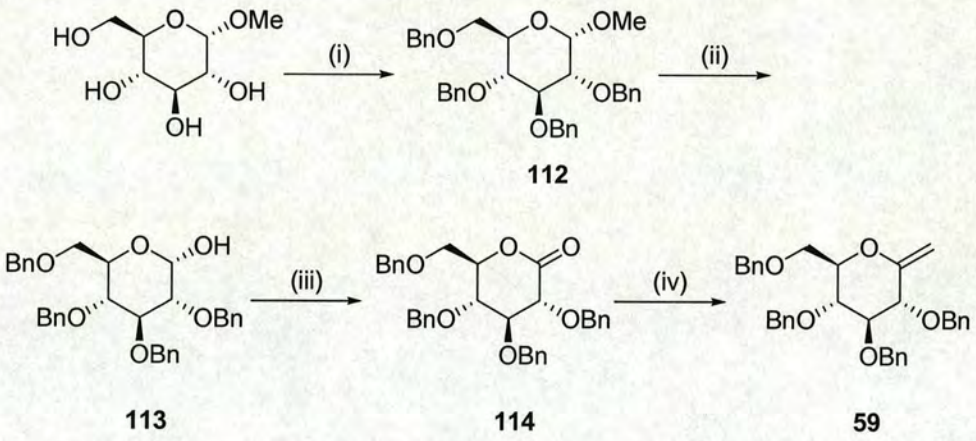


111

2.9.2 Lactone Olefination Approach

In this section the alternative method employed for the generation of exoglycals will be discussed. This approach utilised a series of generic reactions and the procedures will therefore be fully discussed only in the case of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) as a representative example.

2.9.2.1 Synthesis of 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (59)[95d]



i) NaH, BnBr, DMF; ii) AcOH, H_2SO_4, 90°C;
iii) Ac_2O, DMSO; iv) Cp_2TiMe_2, toluene, 70°C

Scheme 2.43

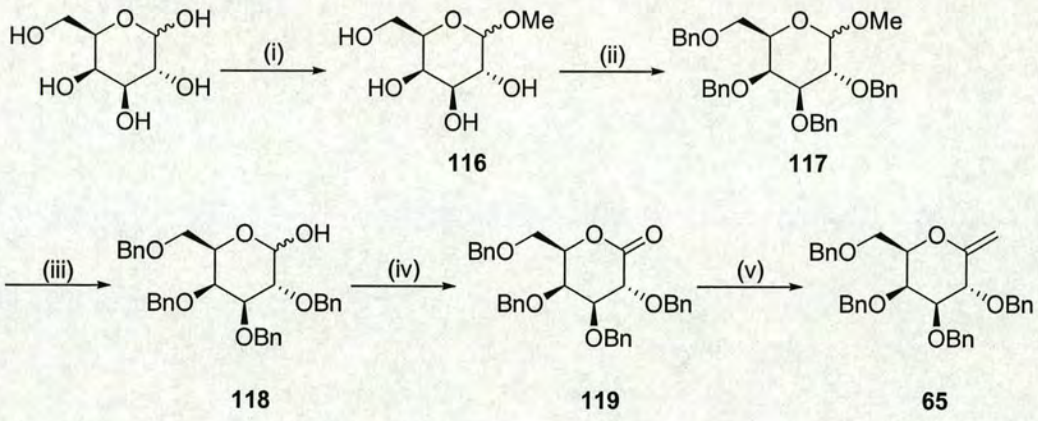
The D-glucose based compound **59** (Scheme 2.43) had the advantage that methyl α-D-glucopyranoside was commercially available as the starting material. In the first step of the synthesis the remaining hydroxyl groups were protected as their benzyl ethers. This was achieved using a standard sugar protection strategy[109] where a solution of the methyl glycoside in DMF was slowly added to a suspension of NaH in DMF. Benzyl bromide was added to the reaction mixture, which was stirred overnight and extracted to give the tetrabenzyl derivative **112** as a crude oil. The oil was purified by chromatography to give the product in 87% yield. It is noteworthy that the crude oil may be carried forward without adversely affecting the quality of the product of the next stage.

The tetrabenzyl compound **112** from the above step was dissolved in glacial acetic acid/sulphuric acid and stirred at 90°C overnight. The reaction mixture was extracted with DCM and the resulting solid recrystallised to give the lactol **113** as a white crystalline solid (35%) that was taken onto the next step.[109] To achieve oxidation of the lactol **113** to lactone **114** an approach via an activated sulfoxonium intermediate was employed involving treatment of the lactone with DMSO/acetic anhydride for 24 h at room temperature.[110] Extraction into DCM gave an oily residue that was subjected to column chromatography to

give the lactone as a colourless oil (76%), which was taken onto the next stage without further purification.

In the final step dimethyl titanocene (**115**) was added to a solution of lactone **114** in toluene and the mixture was stirred in the dark for 24 h at 70°C. On cooling the residue was purified by column chromatography and crystallisation to give the title compound as a white crystalline solid in a 61% yield (14% overall from methyl α-D-glucopyranoside). The title compound was identified by comparison of the ^{1}H and ^{13}C NMR spectra with those in the literature.[111] The presence of the benzyl protecting groups meant that it was not possible to observe the ^{1}H NMR peaks attributable to the methylene group as they were obscured by the benzyl CH_2 signals. However, in the ^{13}C NMR spectrum it was possible to observe the characteristic C-1 and C-2 peaks at 94.1 ppm and 155.7 ppm, respectively. The coupling constant of 7.1 Hz between axial protons 3-H and 4-H indicated that, as expected, the pyranose ring is distorted from the ideal chair conformation.

2.9.2.2 Synthesis of 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-1-enitol (65)



i) AcCl, MeOH; ii) NaH, BnBr, DMF; iii) AcOH, H_2SO_4, 90°C;
iv) Ac_2O, DMSO; v) Cp_2TiMe_2, toluene, 70°C

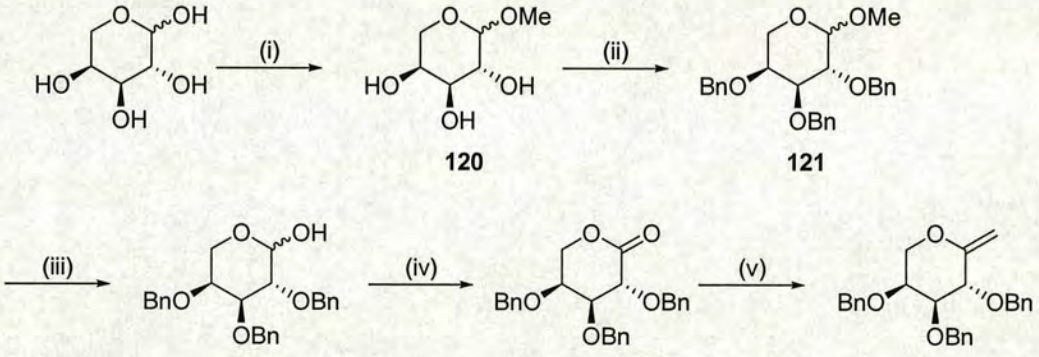
Scheme 2.44

α/β-Methyl galactopyranoside (**116**) (Scheme 2.44) was produced using the method reported by Bennett *et al.*[112] D-Galactose was dissolved in methanolic HCl (prepared by dissolving AcCl in methanol) and the reaction mixture heated at reflux for 7 h, cooled and stored overnight at 0°C. The resulting crystals were filtered, washed with cold methanol and taken

on to the next step without further purification. The conditions for the benzylation were identical to those employed for the glucose derivative **112** and afforded methyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**117**) as a brown oil (78% over 2 steps). This compound was identified by NMR before being taken on to the next stage.

Employing a reaction sequence similar to that used for the glucose analogues **59**, 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**118**) was prepared from the methyl D-galactoside (**117**) as a white crystalline solid (44%). Lactol **118** was then oxidised to the lactone **119** (97%). Petasis olefination of lactone **119** afforded 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-1-enitol (**65**) as a white crystalline solid (40%; 13% overall from D-galactose) using the standard conditions discussed previously. As with glucose analogue **59**, it was not possible to observe the methylene peaks in the proton NMR spectrum, however the characteristic peaks at 94.1 ppm for C-1 and 155.6 ppm for C-2 were observed in the ^{13}C NMR spectrum, these were in good agreement with those found in the literature.[161]

2.9.2.3 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-L-*arabino*-hex-1-enitol (64)



i) AcCl, MeOH; ii) NaH, BnBr, DMF; iii) AcOH, H_2SO_4, 90°C;
iv) Ac_2O, DMSO; v) Cp_2TiMe_2, toluene, 70°C

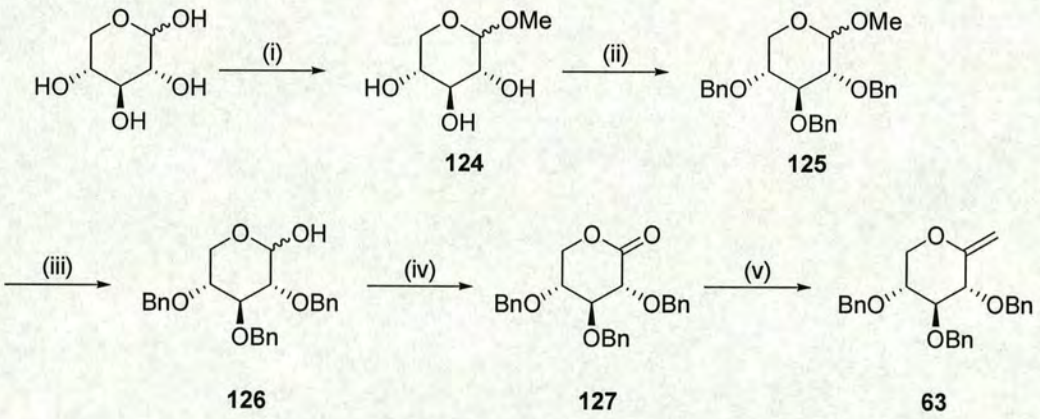
Scheme 2.45

Methyl L-arabinopyranoside (**120**) (Scheme 2.45) was produced using the literature method by Bennett *et al.*[112] The preparation of this compound was identical to that of the galactose analogue **116**, and yielded the intended product as a white crystalline solid that was taken on to the next step without further purification. Employing the same method as for the glucose analogue **112**, methyl 2,3,4-tri-*O*-benzyl-L-arabinopyranoside (**121**) was produced in both

anomeric forms as an oil in a 68% yield over the two steps. The deprotection at the anomeric position was carried out employing sulphuric acid and glacial acetic acid, as before, to give 2,3,4-tri-*O*-benzyl-L-arabinopyranose (**122**) as a brown oil in a 52% yield. The oxidation of the above lactol to 2,3,4-tri-*O*-benzyl-L-*arabino*-1,5-lactone (**123**) used DMSO and acetic anhydride as previously discussed. This resulted in the title compound being produced as a colourless oil in a 96% yield.

Olefination, employing the Petasis reagent **115**, gave the desired 1-methylene sugar, 2,6-anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-L-*arabino*-hex-1-enitol (**64**), as an oil in a 36% yield (12% overall from L-arabinose). The characteristic exoglycal peaks were seen in the carbon NMR spectrum at 97.8 ppm and 155.6 ppm for C-1 and C-2, respectively.

2.9.2.4 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*xylo*-hex-1-enitol (63)



i) AcCl, MeOH; ii) NaH, BnBr, DMF; iii) AcOH, H_2SO_4, 90°C;
iv) Ac_2O, DMSO; v) Cp_2TiMe_2, toluene, 70°C

Scheme 2.46

Methyl D-xylopyranoside (**124**) (Scheme 2.46) was produced in the same manner as the L-arabinose analogue **120**. There was, however, one major difference as on cooling no crystals were formed, therefore, the reaction mixture was neutralised and filtered according to the method of Yoo *et al*[113] to give the title compound as an oil that was taken on to the next stage without further purification.

The reaction conditions used for the next stage paralleled those employed for the glucose analogue **59**. The oil from the previous step gave methyl 2,3,4-tri-*O*-benzyl-D-xylopyranoside (**125**) as a brown oil (52% over 2 steps). Duplicating the deprotection

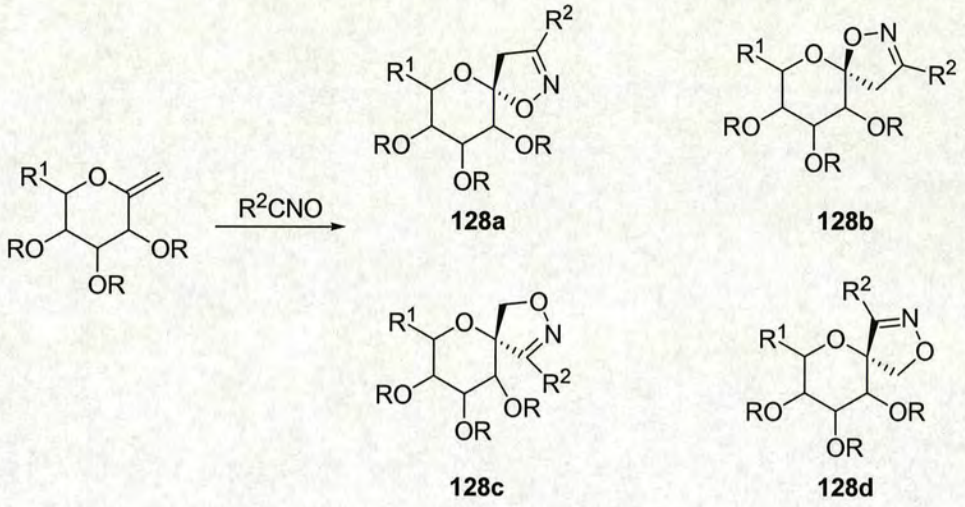
method employed above, 2,3,4-tri-*O*-benzyl-D-xylopyranose (**126**) was produced in a 59% yield as a white crystalline solid. 2,3,4-Tri-*O*-benzyl-D-*xylo*-1,5-lactone (**127**) was synthesised as an oil (78%) from the solid produced in the previous step, using the standard conditions discussed previously.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*xylo*-hex-1-enitol (**63**) was prepared from lactone **127** using the conditions described earlier for analogue **59**. However, in this case there were problems of isolating the exoglycal from the titanocene by-products. As a result an accurate yield was not calculable, however it was possible to see the characteristic peaks attributable to an exoglycal in the ^{13}C NMR spectrum at 86.4 ppm for C-1 and 159.2 ppm for C-2. Therefore, the exoglycal was used for the subsequent cycloaddition reactions without purification.

The procedures described above for the exoglycal synthesis proved to be reliable and three of the four targets were produced on a multigram scale in reasonable yields (12-14% overall from their respective methyl glycoside). The fourth was synthesised, though not isolated due to problems of separation from the titanocene by-products; however this was not a hindrance as the crude mixture could be taken on to the next stage, as discussed later in Section 2.10.8. The main reason for employing these 1-methylene sugars was to use them as easily accessible building blocks for higher monosaccharides. In the course of this work it was concluded that the stability of exoglycals was greater then had previously been suggested.[93] They have a shelf-life of at least two months at 4°C and do not decompose when purified on a silica column. Furthermore, they may be produced on a gram scale.

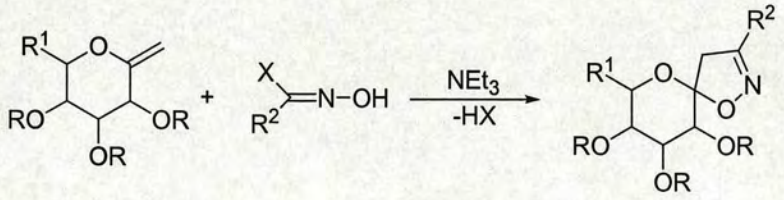
2.10 Cycloaddition Reactions of Exoglycals

Cycloadditions of nitrile oxides to the exoglycals could yield four possible isoxazolines **128a-128d** (Scheme 2.47); i.e. a pair of diastereomers **128a** and **128b** in which the oxygen of the nitrile oxide is linked to the more substituted ring carbon of the exoglycal, and their regioisomers **128c** and **128d**. Formation of **128c** and **128d** was not expected as cycloadditions of nitrile oxides to 1,1-disubstituted alkenes have been reported to afford exclusively 3,5-disubstituted isoxazolines.[3] The regioselectivity of these reactions has been attributed to both steric and electronic effects.[3]



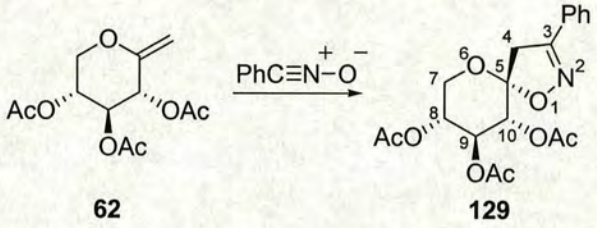
Scheme 2.47

Initial experiments were carried out with peracetylated D-xylose-derived exoglycal **62** using benzonitrile oxide **56** and carbethoxyformonitrile oxide **55** as representative nitrile oxides. The majority of the experiments employed the dehydrohalogentation of the appropriate hydroximoyl halide as used previously (Scheme 2.48), which was modelled on the method of Huisgen.[12,13] However, there were two modifications made to the technique; the first was to have the dipole in excess rather than the dipolarophile (1:1 to 1.4:1). The reason for this change was the longer synthetic sequence required for the exoglycals relative to the nitrile oxide precursors, as a result it was preferable to use excess hydroximoyl halide to ensure the maximum yield of the cycloadducts. The second modification was in the work up where, rather than employing a series of extractions to remove the triethylamine hydrohalide by-product, this compound was removed by filtration. The Mukaiyama method involved dehydration of pyranosyl nitromethanes that was also used for the production of the nitrile oxide in a single experiment.[5]



Scheme 2.48

2.10.1 Synthesis of (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (129)



62 **129**

Scheme 2.49

The cycloaddition (Scheme 2.49) was carried out by the overnight addition of triethylamine in sodium-dried ether to a solution of exoglycal **62** (1 eq) and benzohydroximoyl chloride **68** (1 eq) in dry ether. Work up afforded an oil that yielded on chromatography, in order of elution, unreacted alkene (32%) and the isoxazoline cycloadduct **129** (46%, 76% based on consumed alkene). The recovered exoglycal was sufficiently pure to allow for it to be recycled in future cycloadditions. The product was characterised by ^{1}H and ^{13}C NMR (Table 2.3), mass spectrometry and CHN analysis. Only one isomer was produced as the tlc plate showed a single spot and the NMR spectra indicated the presence of a single compound. The NMR spectra confirmed the presence of the spiroisoxazoline; in the proton spectrum there was a characteristic signal at 3.44 ppm corresponding to the two protons at the 4-position of the isoxazoline ring. This signal appeared as a singlet, but it is noteworthy that the 4-H signals for some of the spiroisoxazolines described later gave an AB pattern. In the carbon spectrum there were characteristic peaks at 43.4 ppm (C-4), 107.2 ppm (C-5) and 157.8 ppm (C-3). The NMR spectra were assigned by comparison with those of the exoglycal precursor and with the reported data of the glucose and galactose based spiroisoxazolines prepared by RajanBabu *et al*[114] and Colinas *et al.*[115] The coupling constants H-8_{ax}/H-9_{ax} 9.6 Hz and H-9_{ax}/H-10_{ax} 10.1 Hz for the sugar ring protons of this cycloadduct indicate that the ring is closer to an ideal chair than the exoglycal **62**.

Table 2.3: NMR data for **129**

Proton	δ_H/ppm	Coupling	*J*/Hz	Carbon	δ_C/ppm
4a, 4b	3.44	4a,4b	nd	3	157.8
7a	3.99	7a,7b	11.2	4	43.4
7b	4.08	7a,8	6.4	5	107.2
8	5.20	7b,8	10.5	7	60.3
9	5.68	8,9	9.6	8, 9, 10	69.0, 69.5, 71.2
10	5.48	9,10	10.1		

The above data were consistent with either the α-anomer **129a** or the β-anomer **129b**. In order to distinguish between the isomers an nOe experiment was carried out on the product **129** where the compound was irradiated at δ 3.44 ppm, the frequency of the 4-H protons. This resulted in not only an 11% signal enhancement between δ 7.66-7.69 ppm for the aromatic region of the 3-phenyl substituent but also a 13% enhancement at δ 5.48 ppm, the peak corresponding to 10-H of the pyranose ring (Figure 2.6). It was concluded, therefore, that the α-anomer **129a** had been produced. If the β-anomer had been formed then the interactions expected would have been at δ 4.08 ppm and δ 5.68 ppm for 9-H and 7b-H respectively. Finally an x-ray crystal structure of this isoxazoline was obtained and it confirmed that the α-anomer had been produced. The details of this crystal structure will be discussed later in Section 2.10.9.

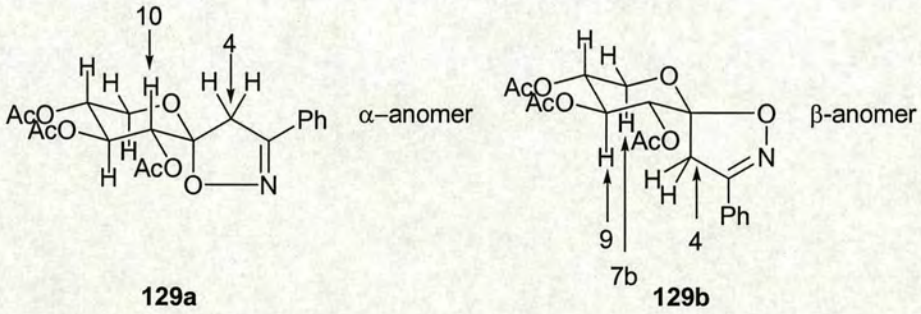
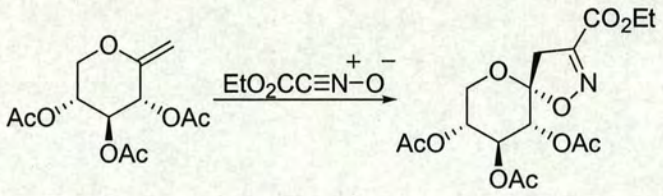


Figure 2.6

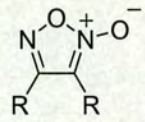
2.10.2 Synthesis of (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (130)



62 **130**

Scheme 2.50

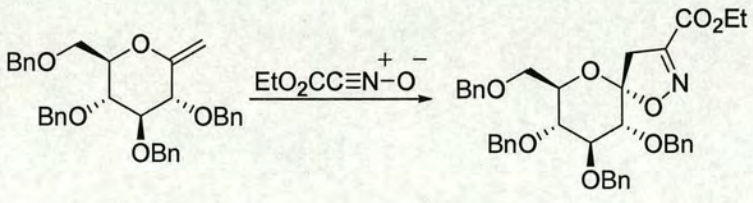
The method was identical to that above although the reactant ratio was altered to 1:1.1 exoglycal to nitrile oxide precursor **67** (Scheme 2.50). The oil produced was subjected to column chromatography to give, in order of elution, recovered exoglycal (48%), an oil that was identified as a single anomer of the title compound (45%, 94% based on consumed alkene), and diethoxycarbonyl furoxan **131a** (23%), which was identified from its ^{1}H NMR spectrum. It was concluded that it was the α-anomer that was present by comparison of the proton and carbon NMR spectra with those of isoxazoline **129**.



131a R = CO_2Et
131b R = Br

Due to the problems previously discussed with regard to the synthesis of acetylated exoglycal **62** an alternative approach was investigated and the following details the cycloaddition reactions of exoglycals produced via the lactone olefination approach.

2.10.3 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (132)



59 **132**

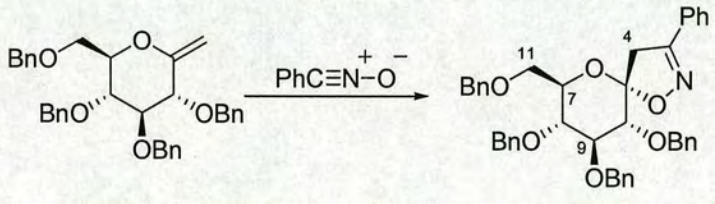
Scheme 2.51

The procedure was identical to those previously described with the triethylamine being added overnight and the nitrile oxide precursor:exoglycal ratio was 1.2:1 (Scheme 2.51). On purification, by column chromatography, the reaction mixture yielded an oil containing solely the title compound as a single isomer (72%, based on consumed alkene), which was identified by comparison of the NMR (Table 2.4) data with those of isoxazoline **130**. The presence of only the α-anomer in the reaction mixture was confirmed by the tlc showing a single spot and there was no evidence of any diastereomeric peaks in either the ^{1}H or ^{13}C NMR spectra. As with the xylose-derived examples (**129**, **130**) the conformation of the pyranose ring was closer to an ideal chair than the precursor **59**; this can be observed in the coupling constants of axial protons 8-H, 9-H and 10-H (H-8/H-9 9.2 Hz, H-9/H-10 9.7 Hz). The NMR data compared favourably to that reported in the literature.[125]

Table 2.4: NMR data for **132**

Proton	δ_H/ppm	Coupling	*J*/Hz	Carbon	δ_C/ppm
4a	3.15	4a,4b	18.4	3	159.5
4b	3.24	7,8	10.2	4	40.9
7	4.26	7,11a	1.8	5	110.3
8	4.00	7,11b	2.7	7	72.2
9	4.30	8,9	9.2	8	76.8
10	3.94	9,10	9.7	9	83.0
11a	3.77	11a,11b	11.3	10	77.7
11b	3.87			11	67.3

2.10.4 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133)



59 **133**

Scheme 2.52

The procedure (Scheme 2.52) was identical to those previously described other than the volume of solvent being increased and the time taken for the addition of the triethylamine was extended to 72 h, this was due to the increase in scale and a wish to limit the concentration of nitrile oxide present in the reaction mixture to inhibit the formation of the furoxan. The exoglycal and the nitrile oxide precursor were in a 1:1.1 ratio. The work up gave some recovered alkene (9%) and the single α-anomer of the title compound as a white crystalline solid (86%, 94% based on consumed alkene), which was characterised by ^{1}H and ^{13}C NMR spectroscopy (Table 2.5), mass spectrometry and CHN analysis. This single anomer was identified as having the α-configuration from the x-ray crystal structure obtained (see Section 2.10.9). The x-ray crystal structure and the proton NMR of this cycloadduct showed that, unlike the exoglycal **59**, the pyranose ring of compound **133** adopted a predominately chair conformation (*J*/Hz 8-9 9.2, 9-10 9.7).

Table 2.5: NMR data for **133**

Proton	δ_H/ppm	Coupling	*J*/Hz	Carbon	δ_C/ppm
4 x 2	3.05	7,8	10.1	3	157.0
7	4.07	7,11a	1.9	4	42.4
8	3.83	7,11b	2.9	5	108.3
9	4.14	8,9	9.2	7	71.8
10	3.74	9,10	9.7	8	77.0
11a	3.58	11a,11b	10.9	9	83.4
11b	3.76			10	77.8
				11	67.4

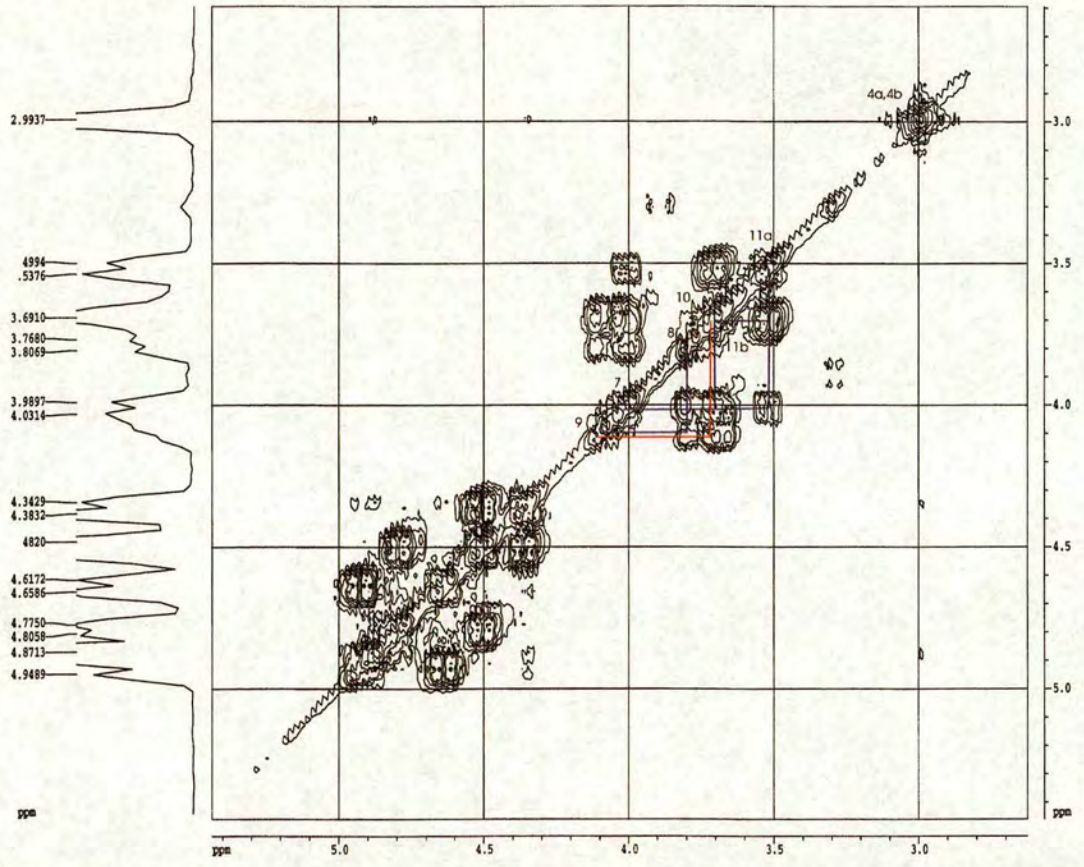


Figure 2.7: COSY Spectrum of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**133**)

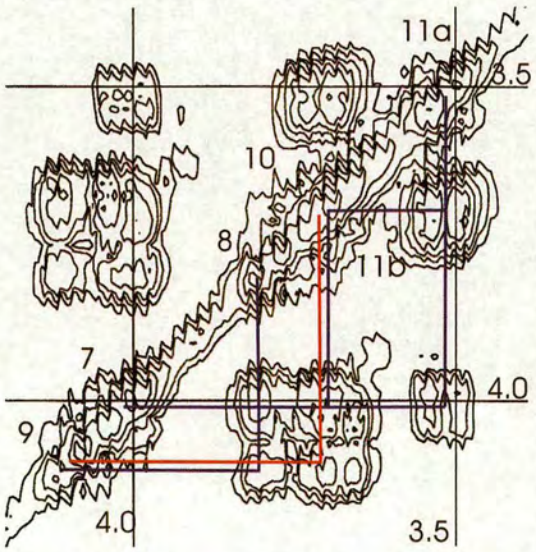


Figure 2.8: Expanded COSY Spectrum Showing the Interactions of the Sugar Ring Protons of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**133**)

It was possible to fully characterise the proton and carbon spectra of the above spiroisoxazoline through the use of COSY (Figures 2.7 & 2.8) and HSQC (Figure 2.9) experiments. The COSY spectrum clearly shows two isolated areas of interaction. The large complex region between 4.34-4.95 ppm shows extensive coupling between the CH_2 groups of the benzyl protection. The other zone between 3.50-4.03 ppm corresponds to the coupling between the protons of the sugar ring. Although analysis of this region is complicated by the overlap of the signals for 10-H and 11b-H a full assignment can be made by reference to the HSQC spectrum. In the COSY spectrum the red line indicates the 9H/10H interaction while the blue lines illustrate the remaining coupling in the sugar ring. Having assigned the proton spectrum it was possible to identify the corresponding carbon peaks from the HSQC spectrum.

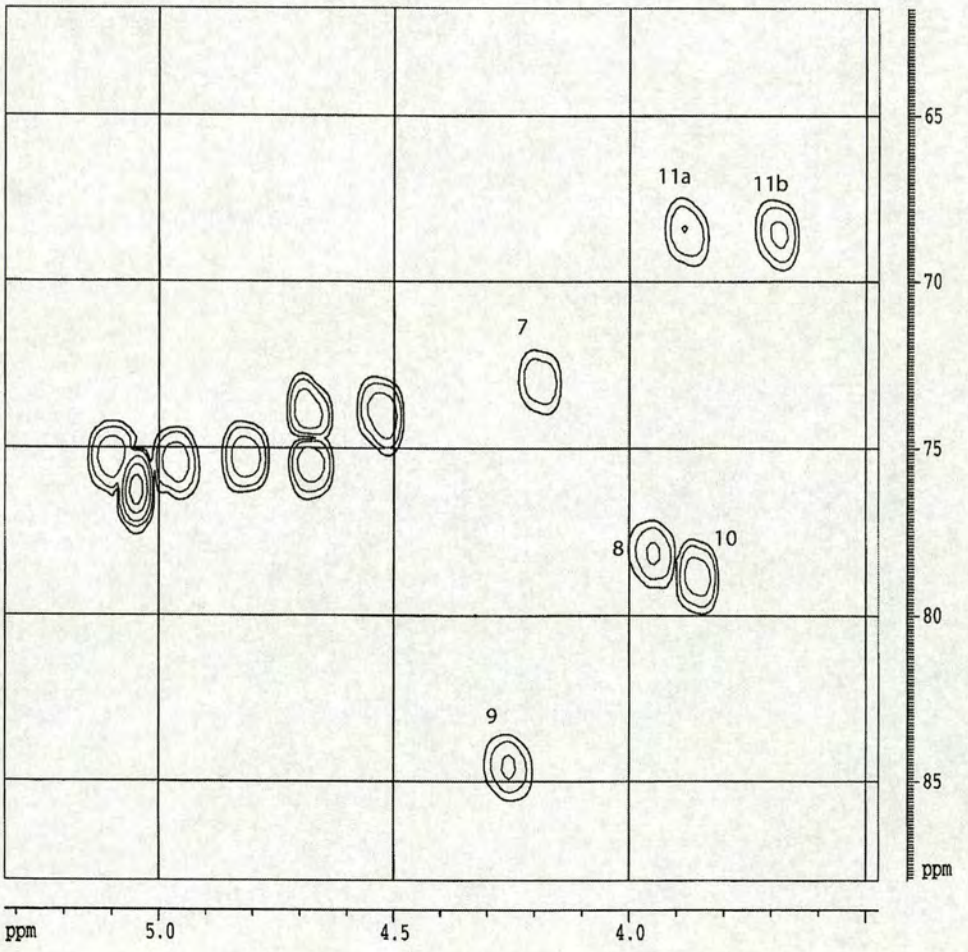
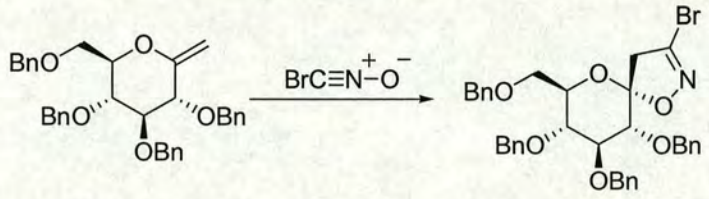


Figure 2.9: HSQC Spectrum of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**133**)

2.10.5 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-bromo-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (134)

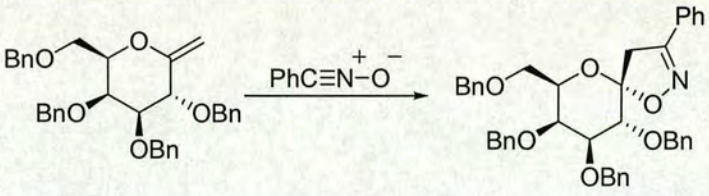


59 **134**

Scheme 2.53

The procedure (Scheme 2.53) was as previously discussed with the ratio of nitrile oxide precursor to exoglycal being 1.2:1 and the addition of the triethylamine taking 18 h. Chromatography of the reaction mixture gave, in order of elution, the title compound as an oil in the α-anomeric form (51%, based on consumed alkene) and the furoxan **131b** as a white solid (31%). It was concluded that the compound had been produced as the α-anomer by comparison of the proton and carbon NMR spectra with those of isoxazoline **133**.

2.10.6 Synthesis of (5*R*,7*S*,8*S*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (135)

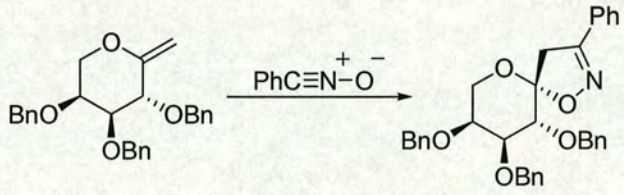


65 **135**

Scheme 2.54

This reaction (Scheme 2.54) was carried out using the experimental conditions previously outlined with the triethylamine added to the reaction mixture over 72 h and the exoglycal to nitrile oxide precursor was 1:1.4. On work up only the title compound was isolated as a white solid (82%, based on consumed alkene), which was characterised by ^{1}H and ^{13}C NMR, mass spectrometry and CHN analysis. It was determined that the isoxazoline was in the α-anomeric form by comparing the NMR spectra with those of isoxazoline **133** and those of (5*R*,7*S*,8*S*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene as reported in the literature.[125]

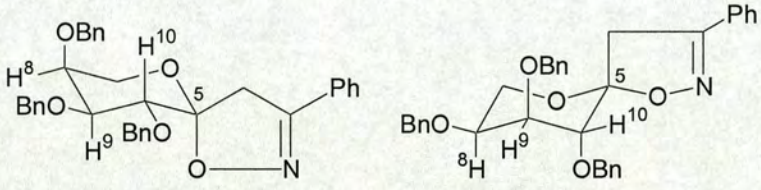
2.10.7 Synthesis of (5*R*,8*S*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (136)



64 **136**

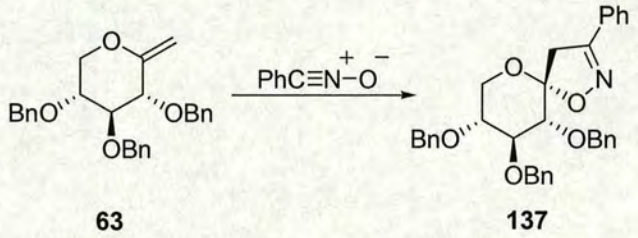
Scheme 2.55

This compound was prepared by cycloaddition of benzonitrile oxide (1.3 eq.) and L-arabinose derived exoglycal **64** (1 eq.). The reaction conditions (Scheme 2.55) were as previously discussed, with the triethylamine slowly added to the reaction flask over 72 h. Work up gave the desired product as a white solid (50%, based on consumed alkene), which was characterised by ^{1}H and ^{13}C NMR, mass spectrometry and CHN analysis. Comparison of the spectra with those of isoxazoline **133** confirmed that it was the α-anomer that had been synthesised. No other products were isolated nor was any starting material recovered. The ^{1}H NMR data for **136** also allowed the preferred conformation for the pyranose ring to be established. The observed couplings for 10-H/9-H (10.0 Hz) and 9-H/8-H (3.0 Hz) are consistent with the $^{8}C_{5}$ conformation **136a** rather than $^{5}C_{8}$ **136b**. The coupling constants also suggest that the sugar ring is a near ideal chair.



136a **136b**

2.10.8 Synthesis of (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (137)



63 **137**

Scheme 2.56

In Section 2.9.2.4 it was noted that the exoglycal **63** could not be isolated from the titanocene by-products, an issue that has been noted by Petasis[97] with regard to the olefination of some compounds using dimethyl titanocene. As a result of the inability to separate exoglycal **63** from the titanocene by-products it was decided to carry the compound through to the next stage of the reaction without further purification. Triethylamine in sodium-dried ether was added to a mixture of benzohydroximoyl chloride **68** and the crude product from the olefination step in dry ether (Scheme 2.56). Following column chromatography the title compound was yielded as an oil (14% over two steps from lactone **127**). This figure was comparable to that of 18% from lactone **123** obtained overall for the analogous L-arabinose **136**. This suggests that the inability to purify the reaction mixture at the exoglycal stage had only a marginal effect on the cycloaddition reaction. The product was characterised by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry, furthermore comparison of this compound's NMR spectra with those of isoxazoline **133** confirmed that it had been synthesised as the single α-anomer.

2.10.9 Structures of the Spiroisoxazolines

Cycloadducts **129** and **133** were isolated from the reactions between benzonitrile oxide and exoglycals **62** and **59**, respectively, as crystalline solids suitable for x-ray analysis. The crystal structures (Figure 2.10 & 2.11) established that the new asymmetric centre, C-5, had the *R*-configuration in both cases, thus confirming the conclusions of the nOe experiments described earlier.

2.10.9.1 (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (129)

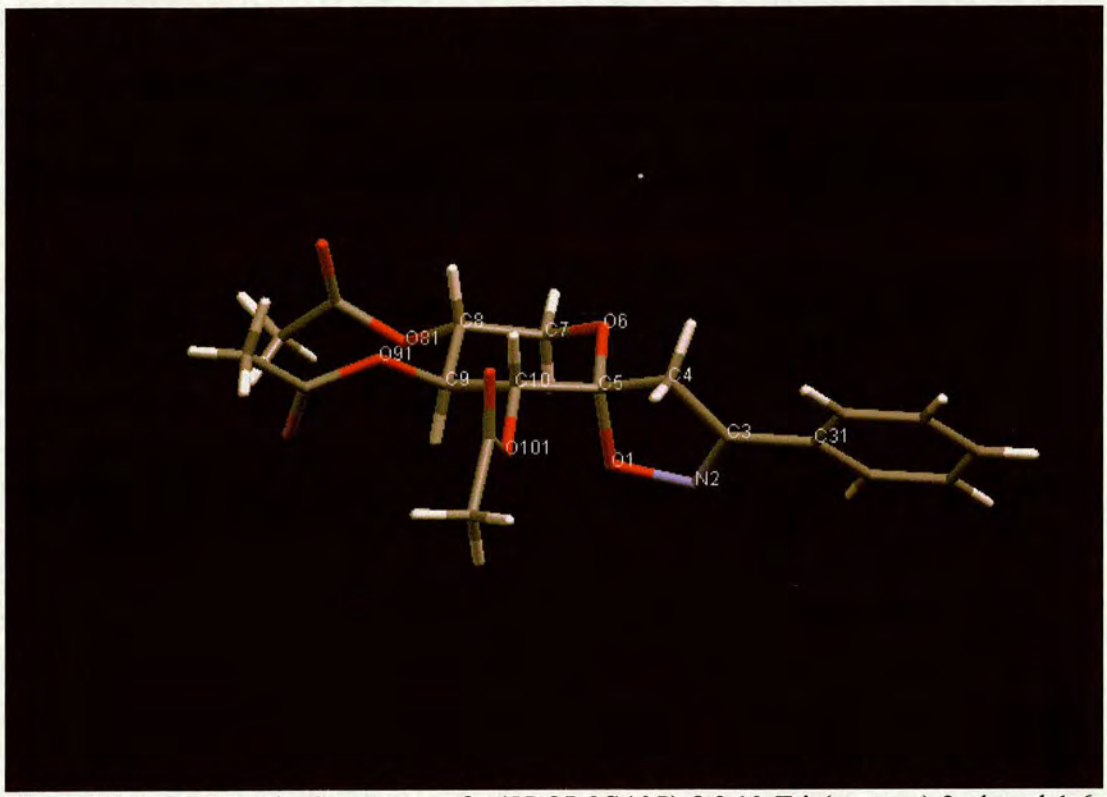


Figure 2.10: Crystal Structure of (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**129**)

The Haasnoot parameterisation of the Karplus equation[116] was employed to calculate the proton-proton coupling constants from the torsion angles taken from the crystal structure, and the results are compared with those found experimentally in solution in Table 2.6. This gave a satisfactory correlation for the data presented. This was unusual as previous work[1,83,87,117] involving sugar isoxazolines indicated that the Haasnoot parameterisation does not always result in good correlation due to the parameters having been determined for a cyclohexane ring with no substituents. Furthermore, the lack of correlation has been attributed in previous cases to the molecule adopting different conformations in the solution and solid phases.[82] This difference in observed and calculated coupling has also been reported for different solvents.[118] In the present case the better correlation may be attributed to the rigidity imparted by the spiro linkage to the isoxazoline.

Table 2.6: Calculated/Observed Coupling Constants for **129**

Protons	θ_{obs}/° [a]	J_{calc}/Hz [b]	J_{obs}/Hz
10,9	-161.68	9.4	10.1
9,8	+161.25	9.4	9.7
8,7a	+130.67(eq)	5.4	6.4
8,7b	-173.14(ax)	10.1	11.2

a. H-C-C-H Torsion Angle (θ) from x-ray data; b. $J_{calc} = 7.76\cos^2\theta - 1.1\cos\theta + 1.4$

The Cremer and Pople puckering parameters[119] (Table 2.7) allow for discussion of the degree to which the isoxazoline and pyranose rings are distorted with respect to their ideal conformations. In this case the pyranose ring has 89% of the puckering of an ideal chair with Q = 0.546Å and θ = 9.9° compared with Q = 0.630Å and θ = 0° for an ideal chair. The low value of θ indicates that the chair, as expected, is in the $^8C_5$ orientation.

Table 2.7: Cremer and Pople Puckering Parameters for **129**

Ring		Q/Å	θ/°	ϕ/°
Pyranose	C(5)-O(6)-C(7)-C(8)-C(9)-C(10)	0.546	9.9	341.1
Isoxazoline	O(1)-N(2)-C(3)-C(4)-C(5)	0.228		142.4

The isoxazoline ring was found to be near planar with a mean deviation from the plane of 0.0936Å (Table 2.8). The ϕ value of 142.4° indicates a mainly envelope conformation (ϕ = 144). This is consistent with most literature isoxazolines, although some have been shown to have structures intermediate between twist (ϕ = 126) and envelope (ϕ = 144).[118] The plane of the phenyl substituent at C-3 on the isoxazoline ring is twisted with respect to the isoxazoline, as shown by the ca. 24° torsion angle out of plane of the isoxazoline.

Table 2.8: Deviation from the Plane of Isoxazoline Ring for **129**

Element	Deviation/ Å
O(1)	+0.1195
N(2)	-0.0388
C(3)	-0.0522
C(4)	+0.1144
C(5)	-0.1430

2.10.9.2 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133)

Figure 2.11: Crystal Structure of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**133**)

The proton-proton coupling constants were calculated from the measured torsion angles of the crystal structure (Figure 2.11) by employing the Haasnoot parameterisation of the Karplus equation.[116] These values are compared with those found in the solution phase from the ^{1}H NMR spectrum in Table 2.9. As with the example above the data presented gave a satisfactory correlation, albeit surprising due to the previous observations that the Haasnoot parameterisation does not always result in good correlation for sugar isoxazolines.[1,83,87,117]

Table 2.9: Calculated/Observed Coupling Constants for **133**

Protons	θ_{obs}/° [a]	J_{calc}/Hz[b]	J_{obs}/Hz
10,9	-174.83	10.2	9.7
9,8	+171.07	10.1	9.6
8,7	-173.07	10.1	10.0
7,11a	-68.49	2.0	1.9
7,11b	+49.76	3.9	2.6

a. H-C-C-H Torsion Angle (θ) from x-ray data; b. $J_{calc}=7.76\cos^2\theta-1.1\cos\theta+1.4$

The Cremer and Pople puckering parameters (Table 2.10) show that in this case the pyranose ring has 91% of the puckering of an ideal chair with Q = 0.556Å and θ = 1.6° compared to Q = 0.630Å and θ = 0° for an ideal chair, and confirms that the chair is in the $^8C_5$ orientation.

Table 2.10: Cremer and Pople puckering Parameters for **133**

Ring		Q/Å	θ/°	ϕ/°
Pyranose	O(1)-C(5)-C(7)-C(8)-C(9)-C(10)	0.556	1.6	64.3
Isoxazoline	O(1)-N(2)-C(3)-C(4)-C(5)	0.182		142.8

The isoxazoline ring was found to be near planar with a mean deviation from the plane of 0.0750Å (Table 2.11), while the ϕ value of 142.8° indicates a mainly envelope conformation (E_5, ϕ = 144),[118] which is comparable to spiroisoxazoline **129**. As with the previous example, the phenyl ring on the isoxazoline was found not to be in the same plane as the isoxazoline ring, which was twisted out of alignment with a torsion angle of approximately 9°.

Table 2.11: Deviation from the Plane of Isoxazoline Ring for **133**

Element	Deviation/Å
O(1)	-0.0957
N(2)	+0.0324
C(3)	+0.0413
C(4)	-0.0917
C(5)	+0.1137

Table 2.12 shows the bond lengths for the isoxazoline rings of compounds **129** and **133**. It may be observed that, when compared, the lengths of both systems are broadly similar. Most

of the bond lengths are also similar to those found for isoxazolines of other sugar systems.[1,82,86] However, the carbon-oxygen bond O(1)-C(5) of the isoxazoline ring was shorter than normal.

Table 2.12: Isoxazoline Bond Lengths of **129** and **133**

Bond **129**	Length/Å	Bond **133**	Length/Å
O(1)-N(2)	1.436(3)	O(1)-N(2)	1.431(3)
O(1)-C(5)	1.436(4)	O(1)-C(5)	1.444(4)
N(2)-C(3)	1.287(4)	N(2)-C(3)	1.281(4)
C(3)-C(4)	1.497(4)	C(3)-C(4)	1.495(4)
C(3)-C(31)	1.481(4)	C(3)-C(31)	1.464(4)
C(4)-C(5)	1.511(4)	C(4)-C(5)	1.506(3)

Selected bond lengths of the two pyranose rings are shown in Table 2.13. As with the isoxazoline rings, the bond lengths show a degree of similarity between the two spiroisoxazolines. When compared to the bond lengths determined for the pyranose rings of other sugar-isoxazoline systems, they were generally found to correspond well, with the exception of C(5)-O(6).[1,83,87,118] The variations for O(1)-C(5) and C(5)-O(6) will be discussed later.

Table 2.13: Selected Bond Lengths of Pyranose Rings of **129** and **133**

Bond **129**	Length/Å	Bond **133**	Length/Å
C(5)-O(6)	1.412(4)	O(6)-C(5)	1.416(4)
C(5)-C(10)	1.533(4)	C(5)-C(10)	1.514(4)
O(6)-C(7)	1.431(4)	O(6)-C(7)	1.445(4)
C(7)-C(8)	1.522(4)	C(7)-C(8)	1.519(5)
C(8)-C(9)	1.512(4)	C(8)-C(9)	1.507(5)
C(9)-C(10)	1.515(4)	C(9)-C(10)	1.517(5)
		C(7)-C(71)	1.511(5)

2.10.9.3 π-Facial Selectivity

A noteworthy feature of this study into the cycloaddition of nitrile oxides to exoglycals is the high level of π-facial selectivity, with only a single product being isolated. The reasons put forward by other researchers for the high selectivity in similar reactions was that the α-face

is less sterically hindered than the β-face,[115] due to the steric bulk of the nitrile oxide[116] and/or the protecting groups on the sugar ring.[120,121] Another possible explanation would be the interactions between the electron lone pairs of the oxygen in the sugar ring and those of the nitrile oxide oxygen that would result from β-face attack. The α-selectivity can also be rationalised in terms of the anomeric effect (Figure 2.12), where the α-anomer is stabilised by the secondary bonding from the lone pair of the sugar oxygen into the low lying σ*-orbital of the carbon-oxygen bond of the isoxazoline. In the β-anomer this donation cannot take place. Furthermore the secondary bonding to the σ*-orbital of the carbon-carbon bond in the β-anomer would result in a decrease of stability as the CH_2 group of the isoxazoline ring would be inductively electron donating.

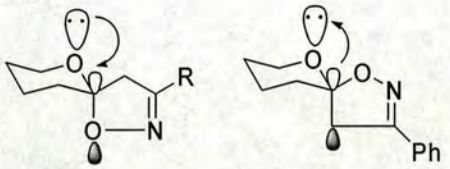
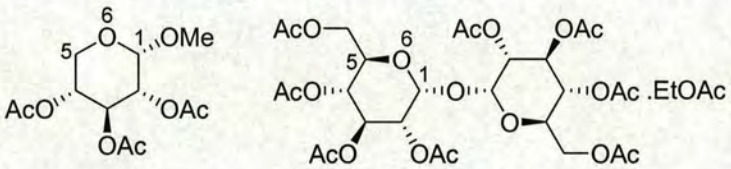


Figure 2.12

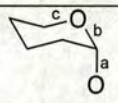


138 **139**

The carbon-oxygen bond lengths for isoxazolines have been quoted in the literature to be in the range of 1.446-1.489Å,[118] while for compounds **129** and **133** this bond length was shorter in both cases, 1.436Å and 1.444Å, respectively. This is surprising as one might expect this bond to be longer in the spiroisoxazoline due to the secondary bonding interaction between the axial lone pair of O(6) and the σ*-orbital of bond O(1)-C(5), thus weakening and lengthening this bond. However, it has been observed that the corresponding bond in glycosides **138** and **139** are also shorter than those of other carbon-oxygen bonds. In addition, both isoxazolines exhibited a shorter C(5)-O(6) bond length than that of O(1)-C(5). These observations suggest that there may be some secondary orbital interactions present in spiroisoxazolines **129** and **133**. Furthermore, when the bond lengths of the two spiroisoxazolines were compared to methyl 2,3,4,-tri-*O*-acetyl-α-D-xylopyranoside **138**[122] (Table 2.14) it was observed that the length of the glycosidic carbon-oxygen bond was much shorter (1.401Å) than the analogous bonds in either of the **129** of **133** at 1.436Å and 1.444Å,

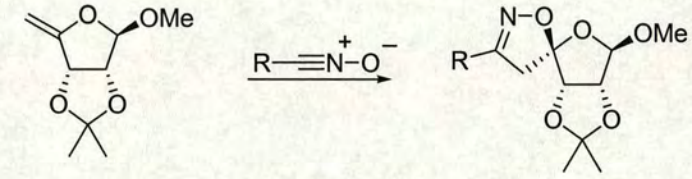
respectively. Also the lengths of the bonds C(1)-O(6) (1.409Å) and C(5)-O(6) (1.426Å) in **138** were both shorter than the corresponding bonds in either **129** or **133**. In the case of trehalose octaacetate ethyl acetate solvate **139**[123] (Table 2.1.4) it was observed that the carbon-oxygen glycosidic bond was considerably shorter than the equivalent bond in the two spiroisoxazolines, while bonds C(1)-O(6) (1.415Å) and C(5)-O(6) (1.438Å) were of comparable length to the analogous bonds in the isoxazolines. These observations imply that the secondary bonding interactions are present in both isoxazolines, **129** and **133**, as well as common *O*-glycosides.

Table 2.14: Specific Bond Lengths of α-*O*-Glycosides/Å

	**129**	**133**	**138**	**139**
a	1.436	1.444	1.401	1.416
b	1.412	1.416	1.409	1.415
c	1.431	1.445	1.426	1.438

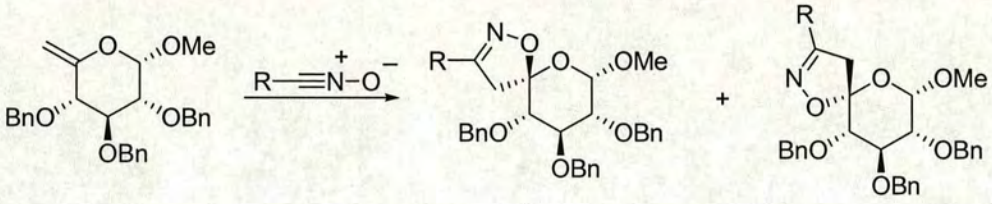
During the course of the present work Gallos and co-workers[120,121] reported the cycloaddition of nitrile oxides to pent-4-enofuranosides **140** and hex-5-enopyranosides **141** (Scheme 2.58). They found that only a single diastereomer **142** was isolated on cycloaddition of a number of nitrile oxides with pent-4-enofuranoside **140**. In contrast to this and the work presented in this thesis, c ycloadditions involving hex-5-enopyranoside **141** afforded two diastereomers, the major product **143a** and a small quantity of **143b** (Scheme 2.57).

The reported explanation for this difference in selectivity was that one face of the furanoside alkene double bond is more hindered than the other; this was attributed to the adjacent isopropylidine group blocking the bottom face. The result of which is that the nitrile oxide attacks the top face of the alkene to give only one diastereomer. However, cycloadditions to the pyranoside were not as highly selective as it has only the more remote methoxy group in an axial position while the remaining substituents are equatorial.



140 **142**

R = 2,6-$Cl_2C_6H_3$, p-Tolyl, Me



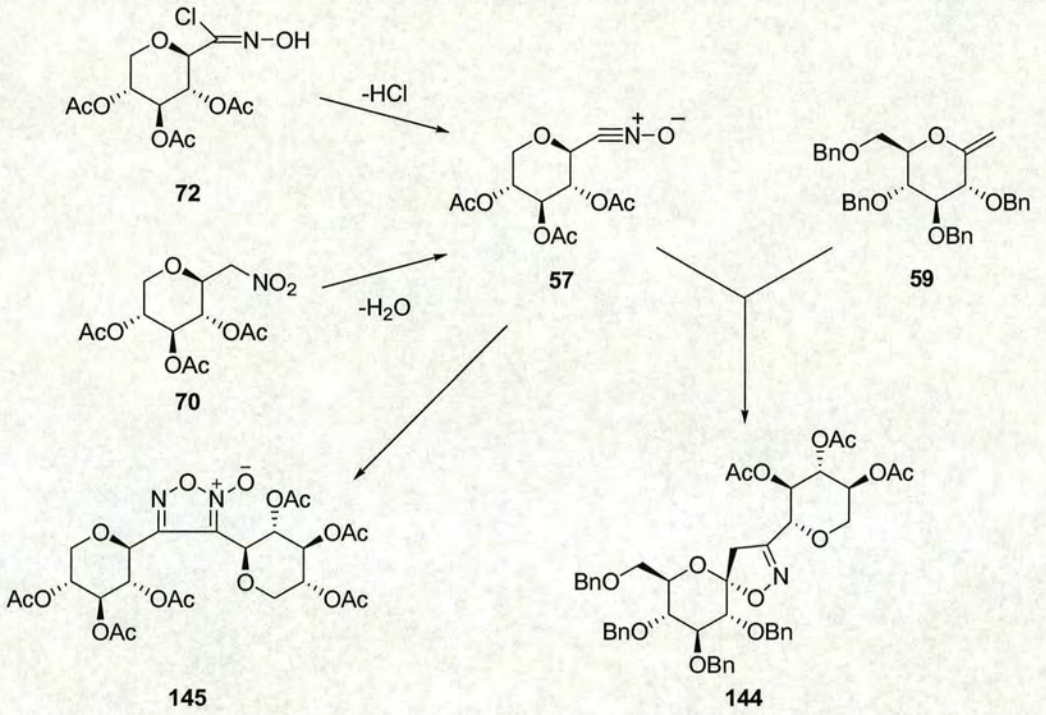
141 **143a** **143b**

R = 2,6-$C_6H_6Cl_2$, Me, Et; 9:1
R = Ph; 17:1

Scheme 2.57

2.10.10 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-(3',4',5'-tri-*O*-acetyl-β-D-*xylo*-pyranos-2'-yl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (144)

Having carried out a number of cycloaddition reactions of non-carbohydrate nitrile oxides to exoglycals the synthesis of a 1,1-isoxazoline linked D-xylose/D-glucose compound **144** was attempted by combination of D-xylose derived nitrile oxide **57** and exoglycal **59**. Similar work has been carried out by this group where D-xylose derived nitrile oxide **57** underwent cycloaddition to hex-5-enofuranose **58**.[124a] Two methods were used to generate the nitrile oxide: dehydrochlorination of hydroximoyl chloride **72**, and dehydration of the pyranosylnitromethane **70**.[124b]



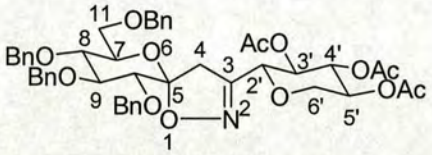
Scheme 2.58

2.10.10.1 The Dehydrohalogenation Approach to the D-Xylose Nitrile Oxide (57)

This reaction (Scheme 2.58) was carried out using the conditions previously described. Hydroximoyl halide **72** (1.2 eq.) and 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (1 eq.) were dissolved in dry ether and the addition of triethylamine in ether was carried out overnight. This resulted in the title compound being produced as a white solid (45%, 72% based on consumed alkene); also isolated from the reaction mixture were unreacted alkene (37%) and the dixylopyranosyl furoxan **145** (15%) that was identified by comparison with an authentic sample (Section 2.10.10.3). The product was characterised by proton and carbon NMR spectroscopy (Table 2.15) and mass spectrometry. It was possible to conclude that only one anomer was present in the reaction mixture as the tlc gave a single spot and there was no evidence of any diastereomeric peaks in either the ^{1}H or ^{13}C NMR spectra.

2.10.10.2 The Dehydration Approach to The D-Xylose Nitrile Oxide (57)

This cycloaddition (Scheme 2.58) was undertaken using the Baker *et al*[124a] modification of the conditions reported by Mukaiyama.[5] The exoglycal **59** (1 eq.) and the pyranosyl nitromethyl compound **70** (1 eq.) were dissolved in dry toluene, and the reaction mixture was heated at 109°C for eight days in the presence of a catalytic amount of triethylamine and tolylene 2,4-diisocyanate. Work up and column chromatography gave the title compound as a white solid (43%, 55% based on consumed alkene), along with recovered exoglycal (24%) and the furoxan **145** (tlc), which was not isolated.



144

Table 2.15: NMR data for **144**

Proton	δ_H/ppm	Coupling	*J*/Hz	Carbon	δ_C/ppm
4a	2.77	4a,4b	17.7	3	156.1
4b	2.90	7,8	9.4	4	41.1
7	3.88	7,11a	1.8	5	108.7
8	3.72	7,11b	nd	7	68.7
9	3.97	8,9	9.2	8	77.4
10	3.57	9,10	9.7	9	83.7
11a	3.47	11a,11b	11.0	10	78.3
11b	3.68	2',3'	9.9	11	68.1
2'	4.39	3',4'	9.5	2'	72.9
3'	4.97	4',5'	9.4	3'	68.7
4'	5.15	5',6a'	10.6	4'	72.5
5'	4.92	5',6b'	5.6	5'	74.1
6a'	3.29	6a',6b'	11.3	6'	66.7
6b'	4.17				

It was possible to fully assign the NMR spectra of this compound by employing COSY (Figure 2.13) and HSQC (Figure 2.14) experiments. The former shows a series of well-defined interactions, and from these all the protons were identified within the two sugar ring

systems. The signals attributable to the glucose ring are clustered between 3.6 ppm and 4.1 ppm, while those signals resulting from the xylose ring are more widely spread over three distinct regions between 4.2-4.3 ppm, 5.0-5.3 ppm and a single signal at 3.4 ppm. The red lines indicate the interactions within the glucose unit and the blue lines illustrate the couplings between the protons of the xylose ring. The AB pattern of the isoxazoline protons may be clearly observed at ~2.7-3.0 ppm. It is also possible to observe the coupling between the CH_2's of the benzyl protecting groups between 4.50-4.78 ppm. The HSQC allowed for the identification of all the signals in the carbon spectrum in particular the isolation of the peaks attributable to the CH_2 groups of the protection strategy from the sugar rings.

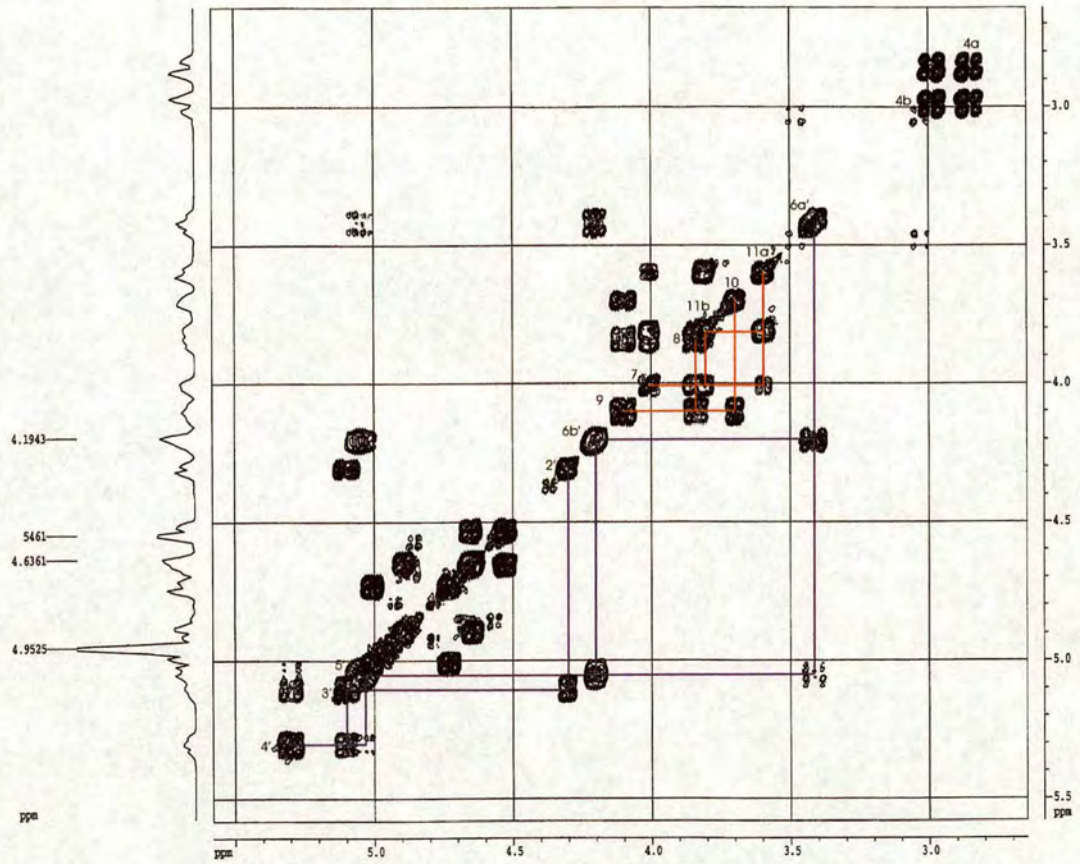


Figure 2.13: COSY Spectrum of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-(3',4',5'-tri-*O*-acetyl-β-D-*xylo*-pyranos-2'-yl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**144**)

It was not possible to state absolutely which anomer had been produced though it was probable, by comparison with the NMR spectra of spiroisoxazoline **133**, that the α-anomer was produced. The ^{13}C NMR spectrum of **133** gave signals for C-4 and C-5 at 42.4 ppm and

108.3 ppm, respectively that were similar to those values observed for disaccharide **144**. The ^{1}H NMR indicated that the pyranose ring of the spiroisoxazoline was less distorted than exoglycal **59**, this was observable from the coupling constants of protons 8-H, 9-H and 10-H being close to that of 10 Hz for an ideal chair conformation (H-8/H-9 9.2 Hz, H-9/H-10 9.7 Hz).

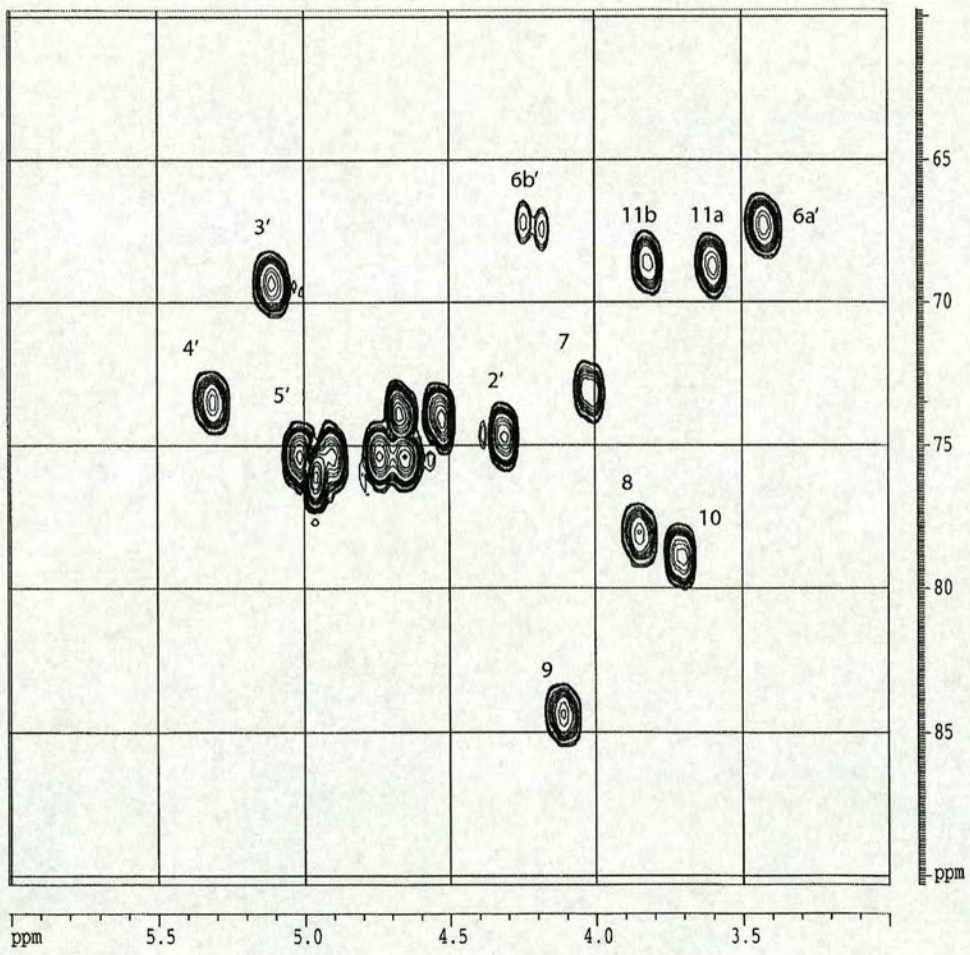


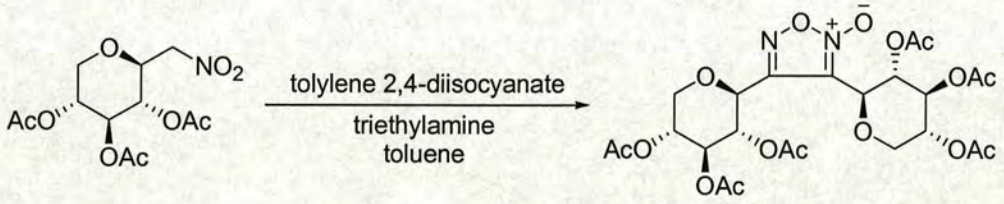
Figure 2.14: HSQC Spectrum of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-(3',4',5'-tri-*O*-acetyl-β-D-*xylo*-pyranos-2'-yl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**144**)

The reason for examining both methods to the *C*-disaccharide was to identify the most efficient approach for the production of this compound. When comparing the two reactions it was useful to examine the yields with respect to the amount of alkene consumed. In the case of the hydroximoyl chloride method the yield, based on consumed alkene, was very good

while with the Mukaiyama method the yield was at best moderate as more alkene was consumed by the Mukaiyama reaction, while producing less disaccharide.

In conclusion, it has been shown that there are two potential approaches for the regio- and stereo-specific synthesis of novel *C*-disaccharides. Furthermore, it may be observed that the hydroximoyl halide was superior with regard to the efficient synthesis of *C*-disaccharides from exoglycals as it may be considered to be less destructive to the thermally unstable exoglycals.

2.10.10.3 Synthesis of 3,4-Di-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazol 2-oxide (145)



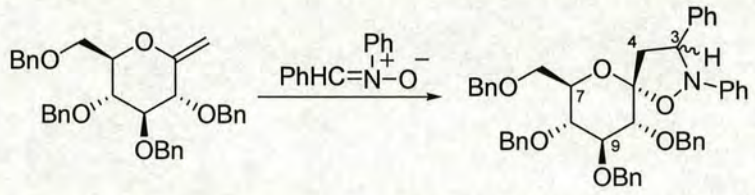
70 **145**

Scheme 2.59

This furoxan (Scheme 2.59) was prepared to allow for the identification of the by-product from the synthesis of the *C*-disaccharide produced above. The Mukaiyama dehydration method was employed where nitromethyl xylose **70** (1 eq.) was heated in toluene (80°C) for eight days in the presence of tolylene 2,4-diisocyanate (3 eq.) and a catalytic amount of triethylamine. This afforded the furoxan as a white crystalline solid (67%), which was identified by comparison of its ^{1}H and ^{13}C NMR spectra with those in the literature.[124b]

In conclusion, it was possible to synthesise a series of spiroisoxazolines in moderate to good yields. Although a number of intermediates were required of the Petasis olefination route it was considered to be a more efficient route to the 1-methylene sugars in a multigram scale. The lack of reproducibility of the carbene method along with the low scale of the reaction made it prohibitively time consuming. It has also been conclusively proven that exoglycals are excellent dipolarophiles for a variety of nitrile oxides.

2.10.11 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-2,3-diphenyl-1,6-dioxa-2-azaspiro[4.5]decane (146)



59 **146**

Scheme 2.60

In an effort to expand the scope of 1,3-dipolar cycloaddition to exoglycal dipolarophiles it was decided to explore the cycloaddition reaction of nitrone dipoles. This approach may provide a complementary route to β-hydroxy ketones and γ-amino alcohols (Scheme 1.16).[22] *N*,α-diphenylnitrone was chosen as a readily available representative example for this study.

A solution of exoglycal **59** (1 eq.) and *N*,α-diphenylnitrone (2 eq.) in sodium-dried toluene was heated overnight, at reflux (Scheme 2.60). Concentration and column chromatography afforded an oil that contained the title compound as two inseparable diastereomers (56%, based on consumed alkene). The moderate yield was probably due to the heating of the reaction mixture causing the degradation of the exoglycal prior to cycloaddition. The title compound was characterised by proton and carbon NMR spectroscopy (Table 2.16) and mass spectrometry. The ^{13}C NMR spectrum provided evidence for the presence of a pair of diastereomers as there were two peaks assigned to C-4 at 48.0 ppm and 53.3 ppm. There was also an indication of other carbons exhibiting two diastereomers but it was not possible to fully assign the spectrum and identify them. There are eight possible products from the above cycloaddition reaction. However, four of these may be discounted as it has long been accepted that the cycloaddition of a nitrone to a 1,1-disubstituted alkene is regiospecific yielding only 5,5-disubstituted isoxazolidines.[3] The four remaining isoxazolidines, **146a-d**, are due to the formation of two new asymmetric centres at the 3- and 5-positions of the heterocyclic ring (Figure 2.15). Compounds **146a** and **146b** would be produced by attack from the α-face, while β-face selectivity would afford **146c** and **146b**. As in the nitrile oxide work, the anomeric effect is likely to promote attack of the nitrone from the α-face of the exoglycal. Therefore, it is probable that in this case the oxygen of the nitrone would attack the alkene at the most substituted terminus to afford the α-anomer. However, the possibility of the β-anomer cannot be eliminated. Indeed, other researchers have suggested that the

cycloaddition of a nitrone to an exoglycal can result in attack from both the α- and the β-faces of the methylene unit to afford two anomers of the 5,5-disubstituted isoxazolidine in the 3*R* conformation.[125] On the basis of the nitrile oxide cycloadditions discussed previously it was presumed than the nitrone had attacked from the α-face to yield the α-anomers, **146a/146b**. From the carbon spectrum it was possible to estimate that the diastereomeric ratio was ~1:3.

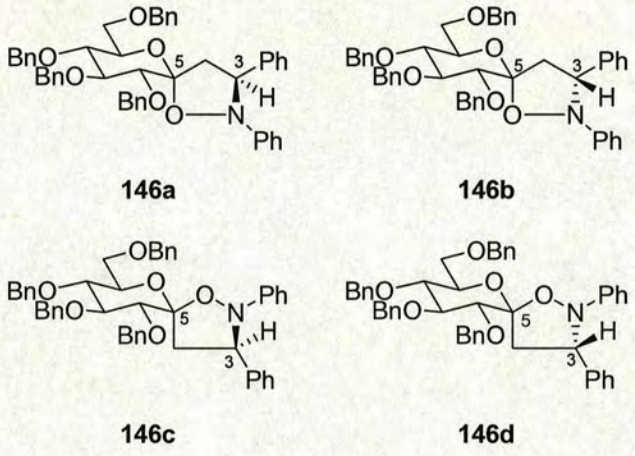


Figure 2.15

Table 2.16: NMR data for **146**

Proton	δ_H/ppm	Carbon	δ_C/ppm
3	4.59	3	70.0
4a	1.86	4 (2 diastereomers)	48.0, 53.3
4b	1.87	9	84.3
7	4.13-4.24	7, 8, 9, 10 (2 diastereomers)	70.0, 72.0, 73.6, 74.3, 75.8, 78.2
8, 10, 11a, 11b	3.66-3.90	CH_2Ph, 11 (2 diastereomers)	68.0, 68.3, 70.6, 72.4, 73.2, 73.6, 74.9, 75.3, 75.5
9	4.31-4.40	5	104.4

In conclusion, this cycloaddition afforded two diastereomeric isoxazolidines from a possible eight, in moderate yield. The regio-chemistry of the cycloadduct was as expected, as was the stereochemistry at the anomeric position. The lack of stereoselectivity at the 3-position was not unexpected by comparison with the literature.[3] This reaction potentially provides an alternative route into the γ-amino alcohol and the β-hydroxy ketone. However, the lower

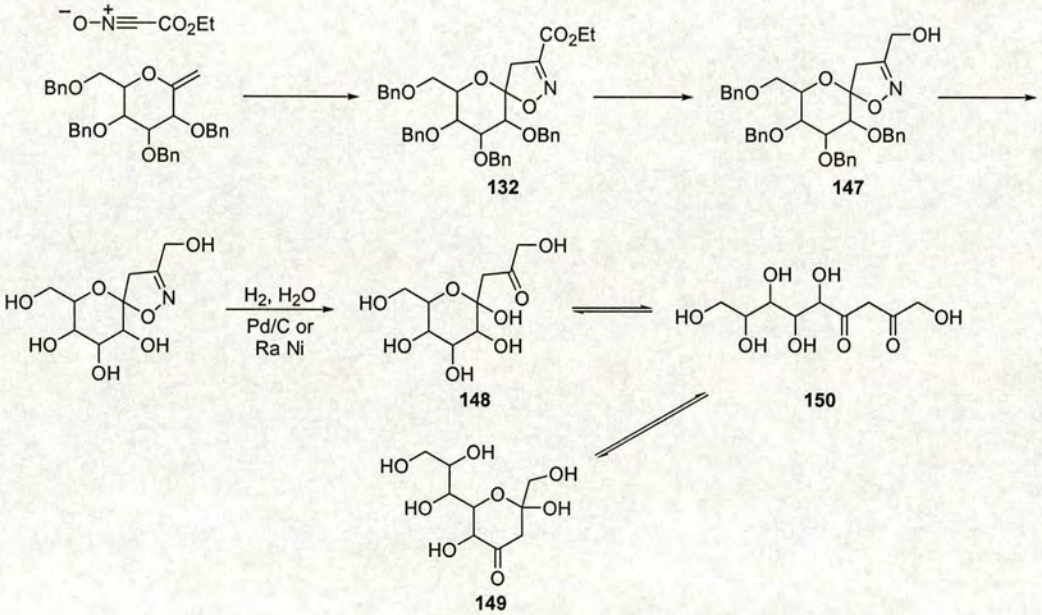
yield suggests that the nitrile oxide route is better suited to the synthesis of higher monosaccharides, therefore, it was not pursued further.

2.11 Reactions of Cycloadducts

Having produced a number of spirioisoxazolines in the previous section it was decided to attempt further reactions on the pathway to ulosonic acid analogues, as discussed earlier (Scheme 2.32).

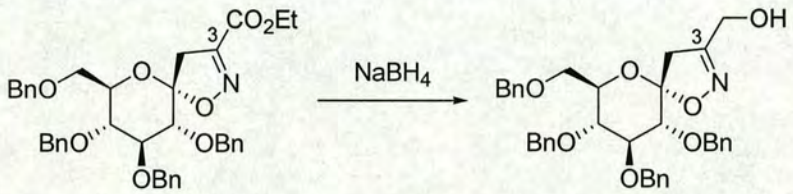
2.11.1 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-hydroxymethyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (147)

The carbethoxy group of isoxazoline **132** was to be reduced to the corresponding primary alcohol **147** as it was thought that the isoxazoline ring would be stabilised to reductive hydrolytic ring cleavage by resonance with the carbonyl of the ester **132** in a similar fashion to isoxazoline **82**. Therefore, it was decided to reduce the ester **132** to the alcohol **147** prior to deprotection and ring opening to β-hydroxy ketone **148**. It was hoped that this would result in an easily accessible route from ester substituted spiroisoxazolines to ulosonic acid analogues **149** (Scheme 2.61) via open-chain β-hydroxy ketone **150**.



Scheme 2.61

The method selected was based on that reported by De Amici *et al* for 3-ethoxycarbonyl isoxazolines.[88] A solution of isoxazoline **132** in ethanol had 10 eq. of sodium borohydride added portionwise (Scheme 2.62). The reaction mixture was stirred at room temperature and the title compound **147** was isolated by extraction and crystallisation as a white solid (81%). This compound was identified by proton and carbon NMR spectroscopy and by mass spectrometry. The ^{1}H NMR spectrum shows that the ethyl group in the starting material is no longer present. A signal was observed at 4.40 ppm; this singlet was assigned to the CH_2 of the hydroxymethyl substituent at the 3-position of the isoxazoline. Further evidence for structure **147** is provided by a peak in the ^{13}C spectrum at 57.8 ppm, attributable to the CH_2OH group. Furthermore there was no indication of the carbonyl, CH_2 peak or methyl peak due to the carbethoxy group of the starting material.



132 **147**

Scheme 2.62

A single product was isolated, in contrast to the reduction of the 5-(3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (**82**) where two products were formed; this was attributed to the presence of the benzoyl ester protecting group found in cycloadduct **82**.

2.11.2 Ring Opening Reactions

A series of reductive ring openings were attempted using a variety of conditions and catalysts. The test reactions were carried out employing (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (**133**) in order to find the best set of conditions for this manipulation. It was hoped that this would allow access to a variety of ulosonic acid analogues (Scheme 2.63).

2.11.2.1 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Palladium/Charcoal

Isoxazoline **133** and boric acid were dissolved in a solution of methanol, water and THF, to which was added the Pd/C catalyst. The reaction mixture was degassed and left to stir under a hydrogen atmosphere for 48 h. Filtration and concentration yielded a white solid that was identified as the starting isoxazoline **133** (72%), there was no indication that any product had been generated.

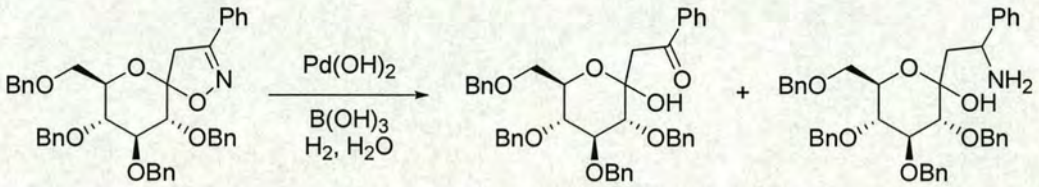
2.11.2.2 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Raney Nickel: Method 1

A solution of isoxazoline **133** in water/methanol was left to stir under a hydrogen atmosphere in the presence of the Raney nickel catalyst for 24 h. Work up yielded the starting material as a white solid (44%), with no evidence of product.

2.11.2.3 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Raney Nickel: Method 2

Isoxazoline **133** was prepared as above, but rather than using a hydrogen filled balloon the hydrogenolysis was carried out at high pressure. The Parr high pressure hydrogenator and Parr 4840 controller unit were used to keep the reaction vessel at 40 bar for 5 h. Work up of the reaction mixture afforded a white solid that was identified as the starting material, isoxazoline **133** (94%). No ring-opened product could be detected in the reaction mixture.

2.11.2.4 Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) Using Pearlman's Catalyst

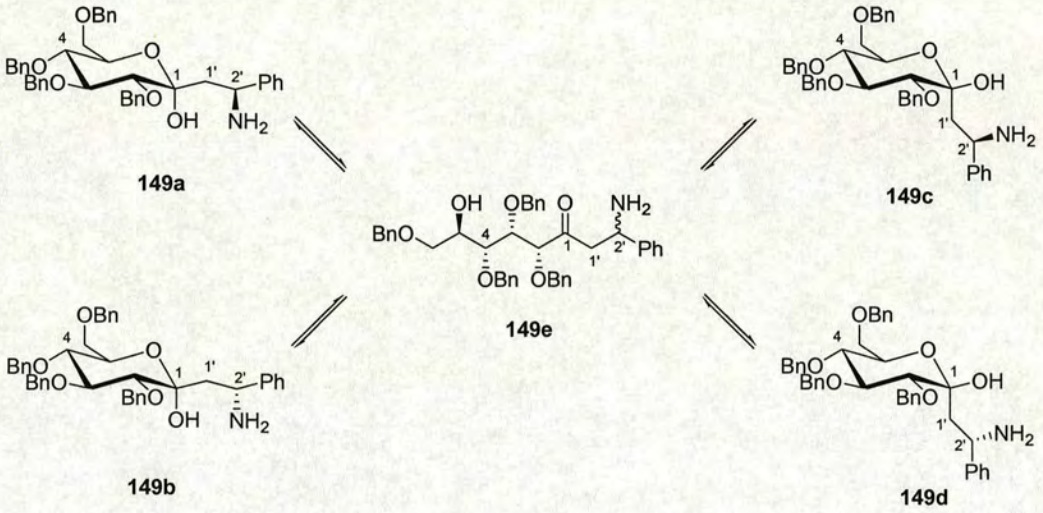


133 **148** **149**

Scheme 2.63

Isoxazoline **133** was prepared as before, then palladium hydroxide on carbon (Pearlman's catalyst) was added and the mixture stirred under an atmosphere of hydrogen for 24 h (Scheme 2.63). Work up yielded only baseline (tlc) material as an oil, which gave a positive test with ninhydrin. This was shown to be 1-(2'-amino-2'-phenylethyl)-2,3,4,6-tetra-*O*-benzyl-1,5-dehydro-D-glucopyranose (**149**) (95% total yield) by ^{1}H and ^{13}C NMR spectroscopy (Table 2.17) and mass spectrometry. No evidence was observed for β-hydroxy ketone **148**.

Five possible structures were considered for **149**: four cyclic hemiketals **149a-d** and the open-chain form **149e** (Scheme 2.65). The ^{13}C NMR provided evidence to support the presence of at least three of the compounds; **149a**, **149b** and **149e**. Signals for the two cyclic forms were observed for only two of the carbons. The first was the $CHNH_2$ group (C-2') adjacent to the phenyl substituent with peaks at 52.3 and 52.5 ppm. The second was the anomeric quaternary carbon (C-1) with peaks at 98.0 and 98.3 ppm. The evidence for an open chain form **149e** was a small quaternary peak at 197.7 ppm, this is the typical frequency for a ketone group. The low intensity of the peak indicated that the open-chain form was a minor component of the equilibrium (Scheme 2.64). This is consistent with the compound being more thermodynamically stable in the ring closed chair hemiketal form. From the carbon NMR it was possible to estimate the ratio of hemiketals **149a** and **149b** to be ~1:1. The 91 MHz ^{13}C NMR spectrum showed other peaks that may be attributable to hemiketals **149c** and **149d** 50.5, 51.2 ppm for C-2' and 97.7 and 100.7 ppm for C-1.



Scheme 2.64

Table 2.17: ^{13}C NMR data for **149**

Carbon	δ_C/ppm
1' (2 diastereomers)	34.1, 35.3[b]
2' (4 diastereomers)	50.5, 51.2, 52.3, 52.5[b]
6	68.8[a,b]
CH_2Ph	73.2, 74.7, 75.3, 75.6[a,b]
1 (4 diastereomers)	97.7, 98.0, 98.3, 100.7[a,b]
2, 3, 4, 5	70.6, 77.1, 78.4, 83.7[a,b]
Ph CH	125.4, 125.8, 126.1[a,b]
Bn CH	127.2-129.0[a,b]
1 open chain form	197.7[b]

a: observed at 63 MHz; b: observed at 91 MHz.

It was presumed that the cyclic hemiketals **149a-d** if formed would adopt the $^4C_1$ conformation. The $^1C_4$ structures, as shown in Figure 2.16, are not likely as these would have all the benzyloxy groups in axial positions and so would be unfavoured relative to the $^4C_1$ conformations where they are all in the more stable equatorial arrangement.

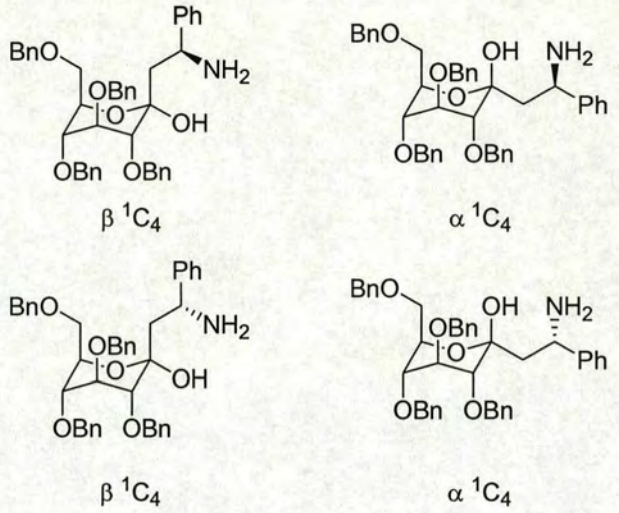
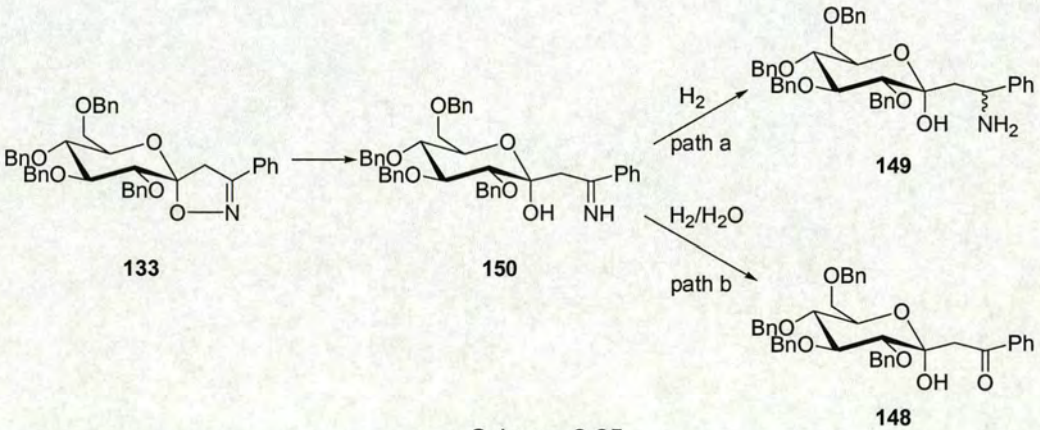


Figure 2.16

The formation of γ-amino alcohol **149** rather than the target β-hydroxy ketone **148** suggests that hydrogenation (Scheme 2.65, path a) of the intermediate imine **150** occurs more readily than hydrolysis (Scheme 2.65, path b) under the conditions used. As the water was added to the above reaction to hydrolyse the intermediate imine,[14,20] the reaction was repeated without water to establish whether the reaction would proceed under anhydrous conditions. As the reaction gave the γ-amino alcohol even in the presence of water it was assumed that the removal of the water would have no effect on the reaction. However, this was not the case as the yield of the reaction was significantly lower without the water, 66% opposed to 95%. The reason for this apparent drop in yield is not known; perhaps the water somehow aided the removal of the product from the catalyst.



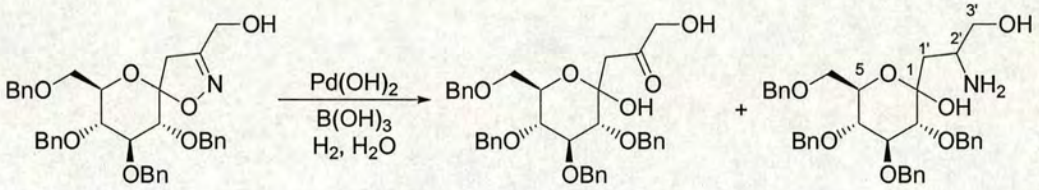
Scheme 2.65

Having found that Pearlman's catalyst successfully cleaved the isoxazoline ring, this was the catalyst of choice for the remaining ring opening reactions.

2.11.2.5 Attempted Reductive Ring Opening of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (132) with Pearlman's catalyst

It was thought that palladium hydroxide might be reactive enough to reductively cleave an ester stabilised isoxazoline ring to afford the β-hydroxy ketone. To this end isoxazoline **132** was prepared for reaction as previously discussed and was stirred, with Pearlman's catalyst, under an atmosphere of hydrogen for 18 h. However, the work up returned only the starting isoxazoline (46%).

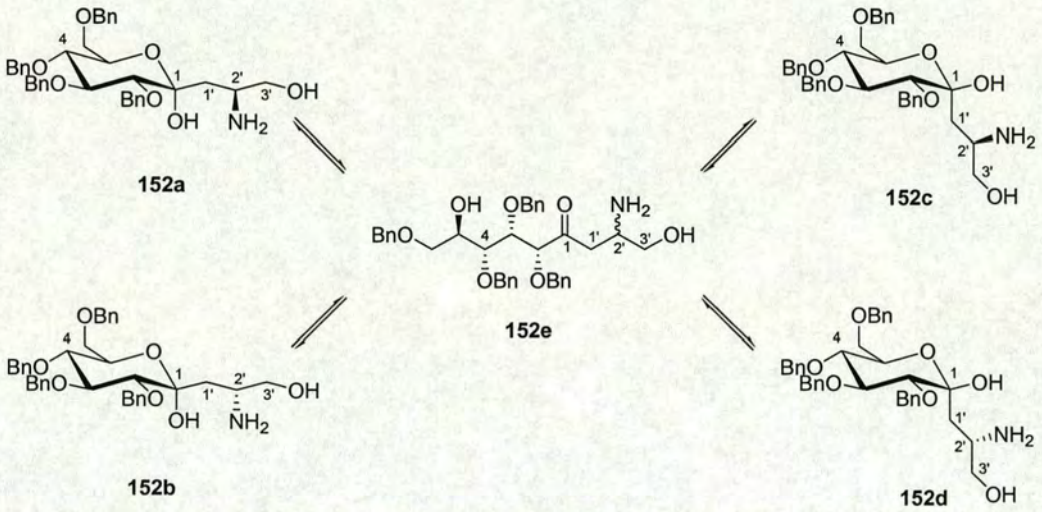
2.11.2.6 Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-hydroxymethyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (147) Using Pearlman's Catalyst



147 **151** **152**

Scheme 2.66

Isoxazoline **147** was stirred under a hydrogen atmosphere in the presence of Pearlman's catalyst for 24 h (Scheme 2.66). Employing the same work up as before, the reaction mixture gave an oil (89%) on the baseline (tlc) that gave a positive test with ninhydrin. On the basis of its NMR spectra and mass spectrometry this was attributed to an inseparable mixture of 1-(2'-oxo-2'-hydroxymethylethyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**151**) and 1-(2'-amino-2'-hydroxymethylethyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**152**) (Scheme 2.67).



Scheme 2.67

The 63 and 91 MHz ^{13}C NMR spectra (Table 2.18) showed distinctive diastereomeric peaks for two hemiketal forms of the γ-amino alcohol. The principal evidence for these diastereomers were two peaks at 50.2 and 50.3 ppm, which were assigned to C-2'. From the carbon NMR spectrum it was estimated that these diastereomers were present in an approximate 1:1 ratio. There was also a small quaternary peak at 210.3 ppm, which is the typical frequency for a β-hydroxy ketone in an open chain sugar,[17] which was assigned as **151**. The NMR evidence is consistent with only two hemiketal forms being present, it is probable that these have structures **152a** and **152b**.

Table 2.18: ^{13}C NMR data for **152**

Carbon	δ_C/ppm
1' (2 diastereomers)	29.6, 30.6
2' (2 diastereomers)	50.2, 50.3
3'	68.4
8	69.5
CH_2Ph	73.2, 74.7, 75.1, 75.5
2, 3, 4, 5	71.0, 78.0, 81.4, 82.9
1	97.6
2' β-hydroxy ketone	210.3

2.12 Conclusions

Two routes for the synthesis of exoglycals were examined; the first was from acetylated nitromethyl xylose **70** via pyranosyl tosylhydrazone **108** using aprotic Bamford-Stevens conditions, the second employed olefination of a pyranosyl lactone employing the Petasis methodology. The former method proved to be unreproducible, however the latter route provided a consistent and reliable approach to pure exoglycals on a gram scale.

Three nitrile oxides were selected to examine the cycloaddition reaction and to ultimately determine its feasibility as a synthetic approach to higer monosaccharides. The three nitrile oxides chosen were bromonitrile oxide, benzonitrile oxide and carbethoxynitrile oxide.

The results of the cycloaddition reactions are summarised in Table 2.19, which illustrates the satisfactory to good yields of the cycloaddition reactions (50-94%). These reactions proved to be a highly stereo- and regio-selective, as in all cases only the α-anomer of the spiroisoxazoline was observed.

Table 2.19: Summary of Cycloaddition Reactions to 1-Methylene Sugars

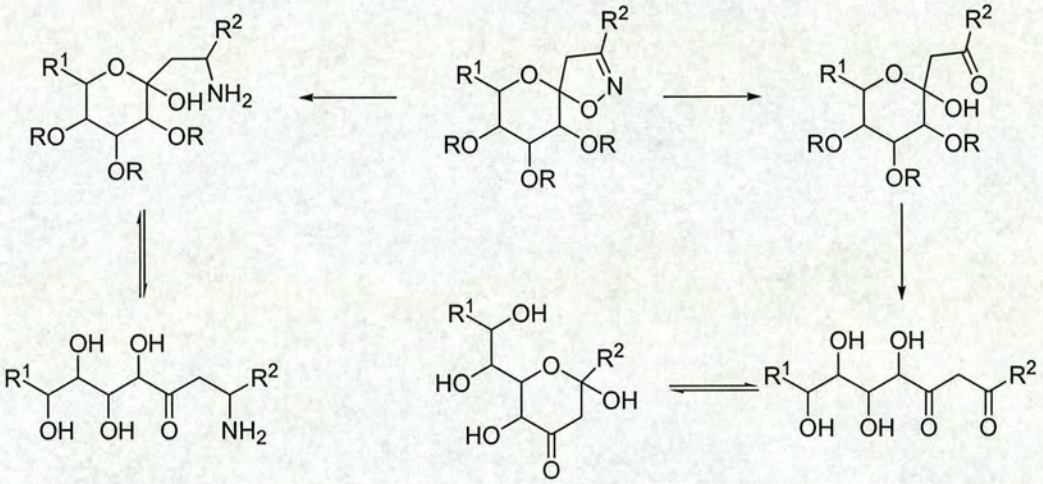
Exoglycal	Nitrile Oxide Precursor	Ratio Dipole: Dipolarophile	Cycloadduct Yield (%)[a]	Recovered Exoglycal (%)	Furoxan (%)[b]
62	**68**	1:1	**129**, 76	32	n/a
62	**67**	1.1:1	**130**, 94	48	23
59	**67**	1.2:1	**132**, 72	n/a	n/a
59	**68**	1.1:1	**133**, 94	9	n/a
59	**66**	1.2:1	**134**, 51	n/a	31
59	**72**	1.2:1	**144**[c], 72	37	15
59	**70**	1:1	**144**[d], 55	24	n/d[e]
65	**68**	1.4:1	**135**, 82	n/a	n/a
64	**68**	1.3:1	**136**, 50	n/a	n/a
63	**68**	n/d[f]	**137**,14[g]	n/a	n/a

a. based on the recovered exoglycal; b. based on the consumption of nitrile oxide precursor; c. dehydrohalogenation method; d. dehydration method; e. furoxan contaminated by base line material; f. crude sample of exoglycal used; g. calculated over two steps from lactone **127.**

In a further illustration of the versatility of this reaction a cycloaddition was carried out to link two pyranosyl systems via an isoxazoline bridge. This was achieved using xylosenitrile oxide **57** generated from either hydroximoyl chloride **72** or pyranosylnitromethane **70**. The nitrile oxide cycloadded to exoglycal **59** to afford spiroisoxazoline **144** in moderate to good yields (55-72%).

Pilot ring opening reactions with spiroisoxazolines **133** and **147** resulted in a mixture of γ-amino alcohols in the case of the former, while the hydrogenolysis of the latter afforded the targeted β-hydroxy ketone as well as the γ-amino alcohols.

2.13 Future Work



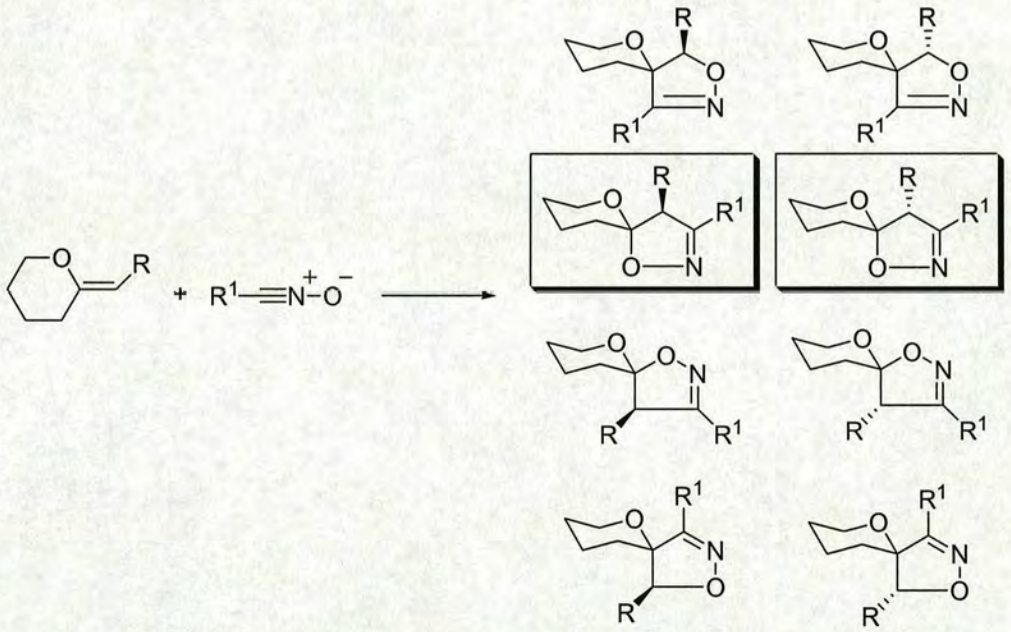
152

Scheme 2.68

The cycloadditions discussed above proceed in good yield and high selectivity. Thus far the ring hydrolytic ring cleavage reactions have afforded the γ-amino alcohols rather than the target β-hydroxy ketones. Therefore, it is required to optimise the hydrogenolysis reaction to afford only the target β-hydroxy ketones. To this end there are a number of catalysts, other than those employed in this body of work, that could be employed for the hydrolytic reductive cleavage of an isoxazoline ring to afford the β-hydroxy ketone and the γ-amino alcohol. These include SmI_2,[126] $TiCl_3$[127] and ozone.[128] The ring opened products must next be deprotected to give access to the potentially biologically active compounds **152** (Scheme

2.68). Once produced the ulosonic acid analogues will be tested against the target biological systems to identify any with inhibitory properties.

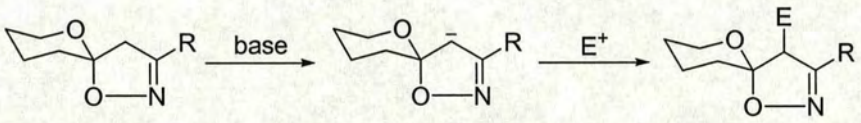
In an effort to expand the range of ulosonic acid analogues a number of approaches may be explored. Alternative nitrile oxides could be employed to afford isoxazolines with different substituents in the 3-position. The substituents of these cycloadducts could then be modified to yield a series of novel isoxazolines. With respect to a specific family of cycloadducts the 3-bromoisoxazolines could undergo a number of substitution reactions to provide access to a number of novel compounds. There is also the possibility that these bromo-cycloadducts could undergo coupling reactions utilising Suzuki conditions or mixed organocuprates. These could, potentially, allow access to a series of spiroisoxazolines for which there are no nitrile oxide precursors available. This work has the potential to be applied to other sugars that will ultimately allow access to a variety of possible drugs, pesticides and herbicides.



Scheme 2.69

There may also be a future in the cycloaddition of nitrile oxides to 1-substituted exoglycals for the production of cycloadducts with three functional groups around the heterocyclic ring. One potential drawback is that the functionality in the 1-position would result in selectivity issues, both regio- and stereo- in the cycloaddition step. However, recent work by Colinas *et al*[115] has shown that the α-anomer diastereomeric pair is favoured (Scheme 2.69). Therefore, it is felt that this may be worthy of future exploration as it may provide an easy route to a

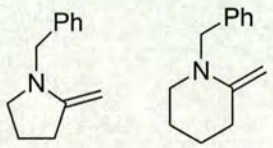
wide range of 4-functionalised 5-membered heterocycles of synthetic value. An alternative route to 4-substituted isoxazolines is to deprotonate the heterocycle with a base then react the resulting anion with an electrophile as described by Jäger *et al* (Scheme 2.70).[129]



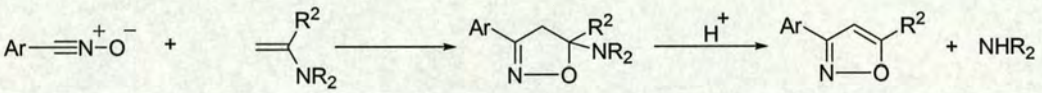
Scheme 2.70

2.14 Iminosugars

It was next intended to apply the chain elongation work from the exoglycals, discussed previously, to enamines that may lead to iminosugars. To this end two model systems were identified for a feasibility study. These were chosen to simulate the two structural forms of the intended sugar compounds. *N*-Benzyl-2-methylenepyrrolidine (**153**) was selected to represent a sugar in the furanosyl form and the pyranosyl analogue was to be based on *N*-benzyl-2-methylenepiperidine (**154**), which may be produced from *N*-benzyl-2-piperidone (**155**). Enamines are known to be highly reactive towards nitrile oxides forming 5-amino-substituted isoxazolines.[130] The previous work in the area has also shown that the initial product can decompose on treatment with acid to give the isoxazole through the loss of the amine (Scheme 2.71). Generally, this is believed to be a useful method to produce 5-substituted isoxazoles.[3] Having proved the principle of the reaction pathway it was then intended to apply this work to a sugar system. For example, enamine **156** might afford iminosugar **157** in a 5-step reaction sequence via spiroisoxazoline **158** as illustrated in Scheme 2.72. Furthermore, exposing isoxazoline **158** to acid might also be expected to afford aminotetrosyl substituted isoxazole **159**.

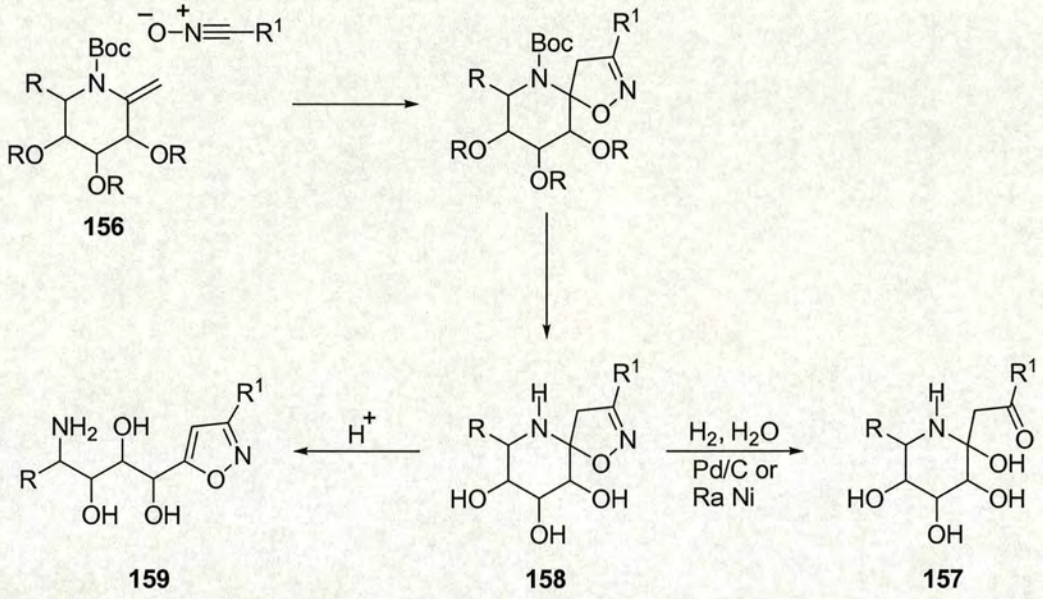


153 **154**



Scheme 2.71

As stated previously it was decided to examine the potential of this approach by testing the reactions on two model systems. It was found by Petasis *et al*[96] that dimethyl titanocene (**115**) will react with lactams albeit at a lesser rate than their lactone analogues, although some difficulty was encountered in the isolation of the enamine products from the titanocene by-products by precipitation, distillation or chromatography. However, it was anticipated that, if this problem did arise in the present work, the enamine could be taken on in a reaction without purification.

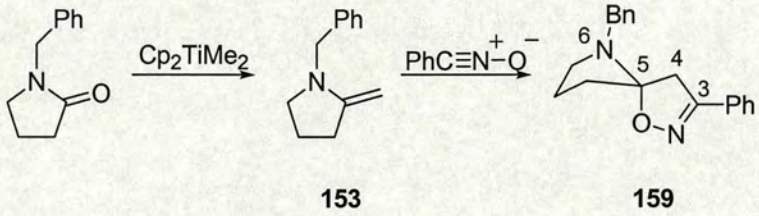


Scheme 2.72

2.14.1 Feasibility Study Employing Model Systems

It was decided that the two model enamines, *N*-benzyl-2-methylenepyrrolidine (**153**) and *N*-benzyl-2-methylenepiperidine (**154**), should be reacted with benzonitrile oxide, generated by the dehydrochlorination of benzohydroximoyl chloride (**68**).

2.14.1.1 Synthesis of *N*-Benzyl-2-methylenepyrrolidine (153) & 6-Benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene (159)



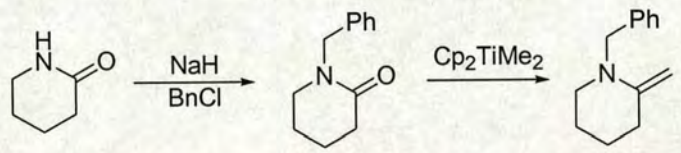
Scheme 2.73

The synthesis of the 5-membered cyclic enamine **153** has been previously carried out by Petasis, although the product could not be purified.[96] *N*-Benzyl-2-pyrrolidinone (1 eq.) was therefore dissolved in dry toluene with the Petasis reagent (2 eq.) and heated overnight

(Scheme 2.73). Concentration of the reaction mixture gave a dark brown-red gum. As found by Petasis the product could not be isolated in pure form. Evidence for the presence of the target enamine **153** in the product was a peak attributable to the methylene group in the ^{1}H NMR spectrum at 4.39 ppm; furthermore peaks could tentatively be ascribed to the remaining protons of enamine **153**. This crude mixture was taken on to the next step without purification.

The crude enamine was dissolved in sodium-dried ether with excess benzohydroximoyl chloride (**68**) (1.1 eq. per equivalent of lactam), the solution was cooled and triethylamine dissolved in dry ether added. The work up was identical to that employed for the exoglycal cycloadditions in Section 2.10 and yielded 6-benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene (**159**) as an impure brown gum (24% from the lactam), which was identified from its ^{1}H and ^{13}C NMR spectra and by mass spectrometry. Despite the impurities observed in the proton NMR spectrum it was possible to identify an AB pattern of a pair of doublets at 3.52 ppm and 3.65 ppm, which were assigned to the CH_2 of the isoxazoline. The major product was identified from the ^{13}C NMR spectrum, with typical quaternary peaks for spiroisoxazolines at 107.4 ppm and 155.7 ppm for C-5 and C-3, respectively. The characteristic CH_2 peak (C-4) was identified at 40.0 ppm; this value was comparable to those of other spiroisoxazolines produced earlier. It is assumed that the pyrrolidine ring of this cycloadduct will adopt an E_5 conformation with the oxygen of the isoxazoline in the pseudo-axial position in order to allow for secondary bonding interactions between the lone pair of the nitrogen and the σ*-orbital of the C–O bond of the isoxazoline ring.

2.14.1.2 Synthesis of *N*-Benzyl-2-piperidone (155), *N*-Benzyl-2-methylenepiperidine (154) & 6-Benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (160)



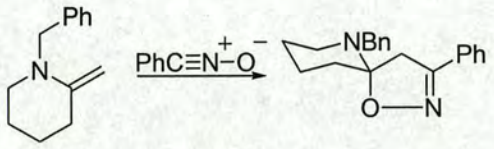
155 **154**

Scheme 2.74

Using a literature method,[131] δ-valerolactam in THF was added to a suspension of sodium hydride in THF (Scheme 2.74). Once the evolution of hydrogen gas had ceased, benzyl

chloride was added to the reaction mixture, which was stirred until no starting material remained. Extraction leads to the title compound **155** as an oil (63%) that was identified by comparison of its NMR with those in the literature.[131]

The methods employed for the conversion of **155** to enamine **154** and isoxazoline **160** were identical to those utilised for the 5-membered analogue (Scheme 2.75). Piperidone **155** and Cp_2TiMe_2 (**115**) were dissolved in dry toluene and heated for 24 h. Work up gave a crude brown gum that when examined using ^1H NMR spectroscopy displayed the peaks required for the enamine **154**, specifically observed was a peak at 4.30 ppm attributable to the methylene protons.



154 **160**

Scheme 2.75

The crude enamine was dissolved with excess benzohydroximoyl chloride (**68**) in dry ether, and triethylamine in dry ether was added to the reaction mixture over 48 h. The reaction was allowed to stir for a further 10 h and on work up the title compound was produced as impure brown crystals (23% from lactam **155**). The product was identified from the proton and carbon NMR spectra and by mass spectrometry. Although the product was not pure, it was possible to assign peaks in b oth NMR spectra to compound **160**. The most characteristic feature of the ^1H NMR spectrum was an AB pattern as a pair of doublets at 3.23 ppm and 3.33 ppm, which were assigned to the CH_2 group of the isoxazoline ring.

2.14.1.3 Conclusions

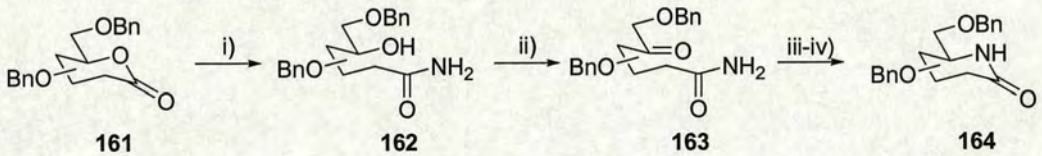
The two *N*-benzyl-enamines **153** and **154** were produced, from the corresponding lactams, as a gum and a brown solid, respectively, both of which contained titanocene by-products. Cycloaddition reactions were successfully carried out between benzonitrile oxide and enamines **153** and **154**. In both cases impure cycloadducts were produced.

The yields of the crude cycloadducts for the two olefination/cycloaddition processes above (**159** 24%, **160** 23%) were marginally better than two of the pyranose analogues, L-arabinose **136** and D-xylose **137**, over two steps. However, they were somewhat poorer than those of the D-glucose **133** and D-galactose **135** analogues. This suggests that the model reactions are proceeding as expected, also it would appear that the lactams are not as unreactive to the Petasis reagent as previously thought. However, the reaction could be improved considerably by purification at the enamine stage.

The model experiments showed sufficient promise that similar olefination and cycloaddition processes might be possible on the analogous sugar systems, in both furanosyl and pyranosyl analogues. However, due to time constraints only the latter was explored and will be discussed below.

2.14.2 Routes to Pyranosyl Lactams

A number of methods for producing sugar lactams can be found in the literature, many of which are long and arduous processes. One of the most effective of these preparations is that employed by Overkleeft *et al* (Scheme 2.76),[36] which is similar to that of Hoos *et al.*[132] In the former method, reaction of lactone **161** with methanolic ammonia afforded hydroxy amide **162**, and the hydroxyl group was then oxidised to the ketone. Keto amide **163** was then converted into lactam **164** by successive treatment with methanolic ammonia and then sodium cyanoborohydride/formic acid. The Hoos approach differed from that of Overkleeft at two stages of the reaction pathway. Firstly, in the cyclisation step where the ring closure was catalysed by acetic acid rather than with ammonia-saturated methanol. Secondly, formic acid and sodium cyanoborohydride were replaced with Et_3SiH and $BF_3.Et_2O$ for the final stage.

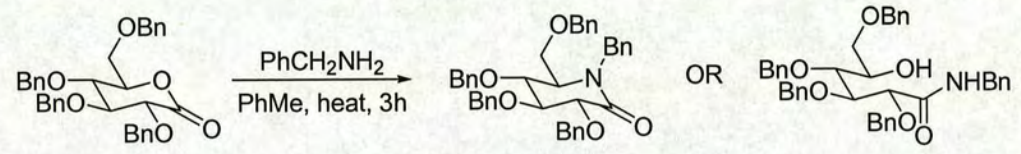


161 **162** **163** **164**

i) NH_3, MeOH; ii) DMSO, Ac_2O; iii) NH_3, MeOH; iv) $NaCNBH_3$, HCO_2H.

Scheme 2.76

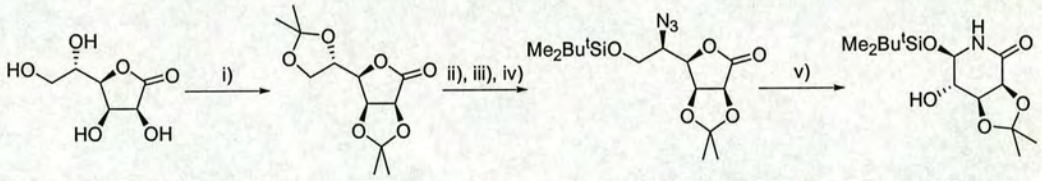
Rajanikanth reported that the glucose derived lactam **165** could be prepared by simply heating the lactone **114** with benzylamine in the presence of 4Å molecular sieves and a catalytic amount of amberlite IR $120H^+$ (Scheme 2.77).[112] However, other workers have failed to reproduce these results; when Fleet *et al.* re-examined this method they only isolated acyclic amide **166**.[133]



114 **165** **166**

Scheme 2.77

Fleet and co-workers also synthesised mannose based lactam **167** from L-gulonolactone **168** (Scheme 2.78).[134] The nitrogen of the ring was introduced by the reduction of azido lactone **169**, which was produced by the selective deprotection of the hydroxyl groups in the 5,6-position and tosylation of the 5-position followed by a nucleophilic substitution employing sodium azide.

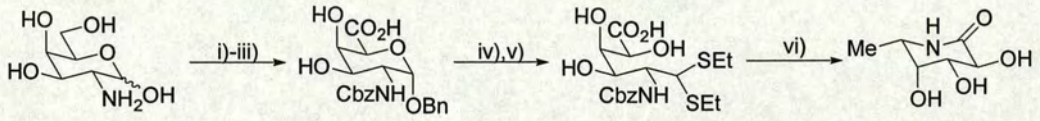


168 **169** **167**

i) acetone, 2,2-dimethoxypropane, TsOH; ii) AcOH, H_2O (7:1); iii) imidazole, $^tBuMe_2SiCl$, DMF; iv) a. $(F_3CSO_2)_2O$, pyridine, DCM; b. NaN_3 DMF; v) H_2, Pd/C, MeOH

Scheme 2.78

A lactam analogue **170** of L-fucose has been produced by Schedler *et al* from the aminosugar D-galactosamine **171** (Scheme 2.79) by hydrolysis and thioacetalisation of glycoside **172**. This was followed by the desulfuration, deprotection and cyclisation of compound **173** with Raney nickel.[135]

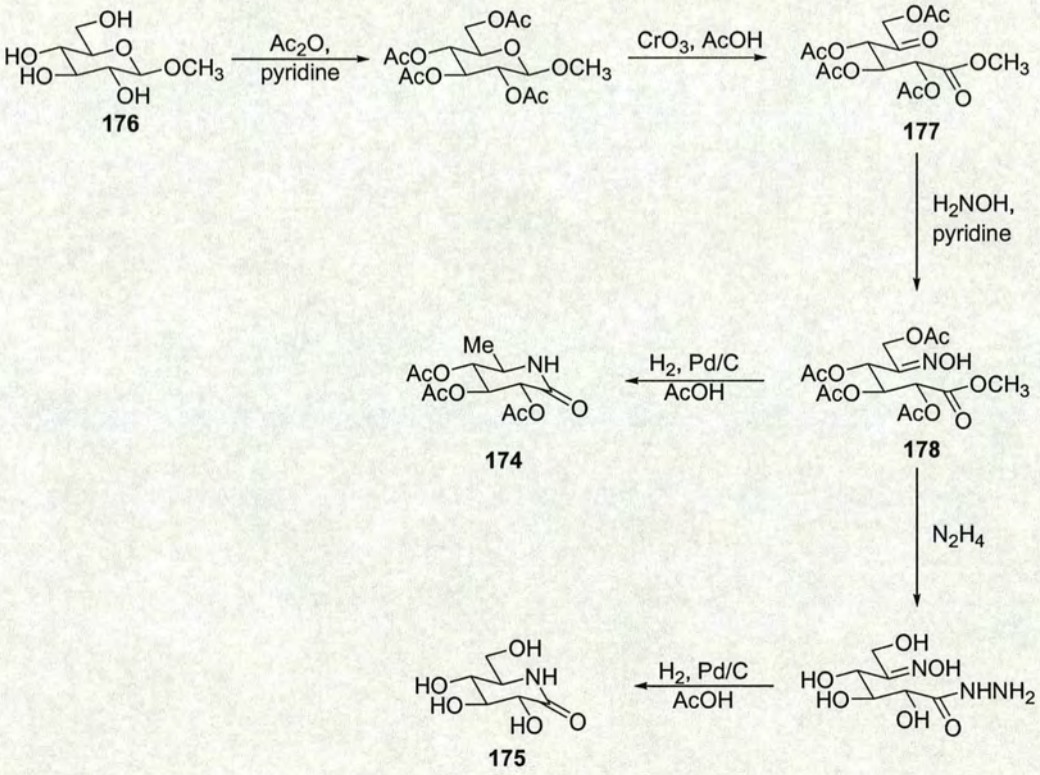


171 **172** **173** **170**

i) CbzCl, H_2O; ii) BnOH, CH_3COCl; iii) Pt, O_2, H_2O-EtOH;
iv) 1:4 TFA:H_2O, 90°C; v) EtSH, HCl; vi) Raney Ni, EtOH

Scheme 2.79

Finally, Pistia-Brueggeman synthesised 5-amino-D-gluconic acid lactams **174** and **175** from methyl β-D-glucoside (**176**) (Scheme 2.80). This was achieved by the oximation of keto-ester **177** with hydroxylamine to afford **178**. Reduction of the oxime yielded lactam **174** by the spontaneous cyclisation of the 5-amine-5-deoxy intermediate. Alternatively, oxime **178** could be converted to lactam **175** by treatment with hydrazine.[136]



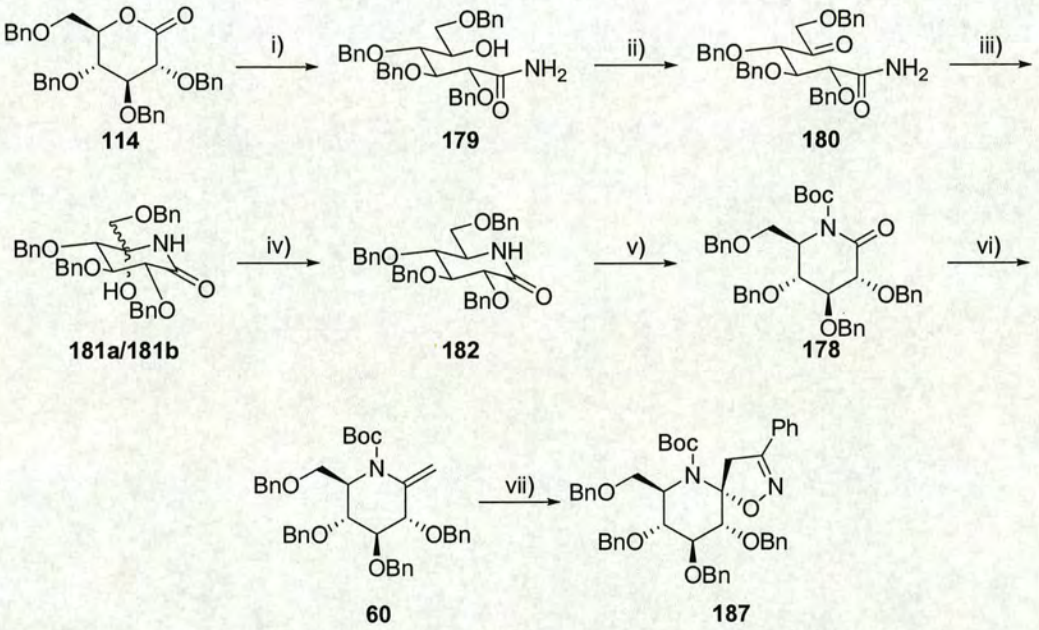
176 **177** **178** **174** **175**

Scheme 2.80

2.14.3 Feasibility Study Employing a Monosaccharide System

Following the success of the two model systems it was decided to apply this chemistry to a monosaccharide framework. A glucose-derived iminosugar was selected as the target as there was a relatively straightforward route from lactone **114** to the corresponding protected lactam **178** (Scheme 2.81).[36]

2.14.3.1 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-*N*-Boc-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (186)



i) NH_3, MeOH; ii) DMSO, Ac_2O; iii) NH_3, MeOH; iv) $NaCNBH_3$, HCO_2H;
v) DMAP, Boc_2O, MeCN; vi) Cp_2TiMe_2; vii) PhClCNOH, NEt_3

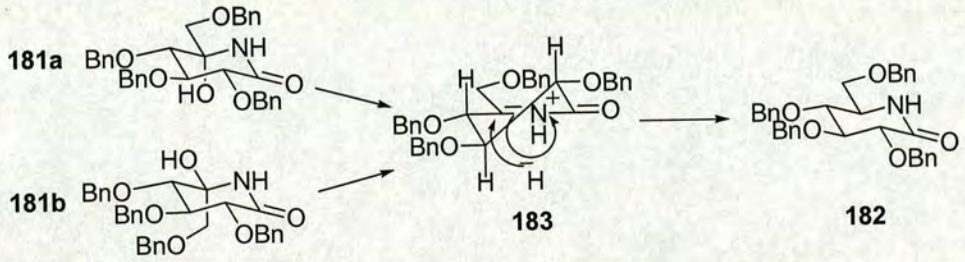
Scheme 2.81

Employing the method described by Overkleeft *et al* (Scheme 2.81),[36] lactone **114** was dissolved in ammonia/methanol solution and left to stir. Concentration and crystallisation of the residue from ethyl acetate and petroleum ether gave 2,3,4,6-tetra-*O*-benzyl-D-gluconamide (**179**) as a white solid (86%) that was taken on to the next step.

Using a modified method from that used by Overkleeft *et al*,[36] gluconamide **179** was dissolved in acetic anhydride and DMSO and the reaction mixture left to stir for 24 h. Work up yielded 2,3,4,6-tetra-*O*-benzyl-5-dehydro-5-oxo-D-gluconamide (**180**) as an oil that was directly taken on to the next stage without further purification.

The 5-oxo-D-gluconamide **180** was dissolved in a solution of ammonia/methanol and the mixture left to stir for 2 h. Column chromatography yielded a mixture of the two lactams, 2,3,4,6-tetra-*O*-benzyl-5-dehydro-5-hydroxy-D-*glucono*- and L-*idono*-lactam (**181a** & **181b**). From the mixture **181a** was isolated by column chromatography as a white solid (31% over 2 steps) leaving **181b** (35% over 2 steps) as an oil. Both products were identified by comparison of their NMR spectra with those in the literature.[36]

The mixture of hydroxylactams **181a** & **181b** was used in the next stage as both afforded the same lactam **182** on dehydration (Scheme 2.82). Hydroxylactams **181a** & **181b** were dissolved in a mixture of acetonitrile and formic acid, to which sodium cyanoborohydride was added. The reaction mixture was refluxed for 2 h, after which it was quenched with hydrochloric acid (0.1 M) and extracted into ethyl acetate. Column chromatography gave 2,3,4,6-tetra-*O*-benzyl-D-*glucono*-δ-lactam (**182**) as a white solid (72%).



Scheme 2.82

The proposed mechanism for the formation of lactam **182** is shown in Scheme 2.82. The acid catalysed dehydration of the two lactams gave the same final product as both reactions proceed through the same intermediate acyliminium ion **183**. The hydride ion then attacks intermediate **183** from the α-face to result in the desired lactam. The lone pair of the nitrogen in lactam **182** is presumed to be axial to the ring as this allows the most potent overlap between the nitrogen lone pair and the π-orbital of the carbonyl (Figure 2.17).[36]

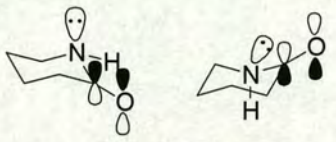
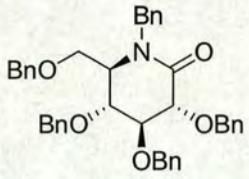
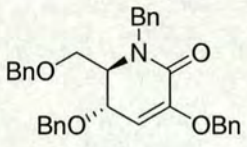


Figure 2.17

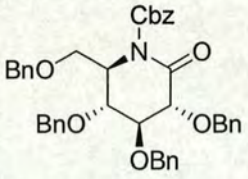
Some problems were encountered in the attempted protection of the lactam nitrogen. The initial technique required the iminosugar to be stirred with potassium hydroxide and benzyl chloride. This resulted in a mixture of the target compound **184** and a by-product, (5*S*,6*R*)-*N*-benzyl-3,4-bis(benzyloxy)-6-benzyloxymethyl-1,2,5,6-tetrahydropyridin-2-one (**185**), as reported in the literature.[132] Both were formed in poor yields 14% and 8%, respectively, and an alternative route was therefore sought. It was attempted to improve this method by adapting that employed for the model system, where the iminosugar was refluxed with benzyl bromide and sodium hydride. This gave only the by-product **185** and none of the target **184** was detected. A third approach was to stir the iminosugar with benzyloxycarbonyl succinimide and triethylamine, however this returned the starting material and the CbzOSuc unreacted, and there was no evidence for the formation of **186**.



184



185

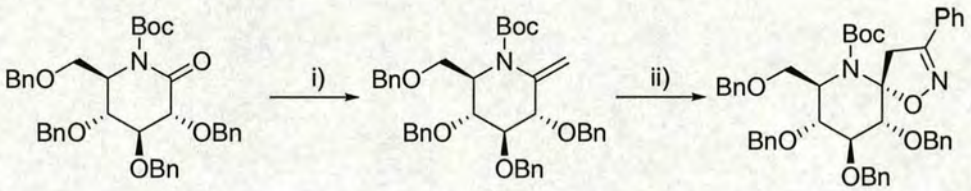


186

Ultimately, the protection strategy adopted utilised a Boc protecting group. The protected lactam **178** was produced by stirring lactam **182** in acetonitrile for five and a half hours in the presence of DMAP and Boc anhydride. Column chromatography yielded the target compound **178** as a colourless oil (46%), which was identified by comparison of its proton and carbon NMR data with those in the literature.[137]

The protected lactam **178**, produced above, was dissolved in toluene and heated in the presence of dimethyl titanocene (**115**) for 24 h (Scheme 2.83). The resulting oil was subjected to column chromatography to give, in order of elution, the target enamine **60** (8%) and unreacted lactam **178**. Due to the impurities present it was difficult to positively identify enamine **60** as the mass spectrum was inconclusive and it was not possible to observe the methylene protons due to the benzyl protecting strategy. The Boc protecting group was

present at 1.49 ppm and visually the spectrum looked very similar to that of glucose analogue **59** with a doublet at 3.89 ppm, a multiplet between 3.60-3.72 ppm for the remaining sugar protons and a second multiplet between 4.41-4.82 ppm that contained the methylene protons as well as the CH_2 protons from the protecting groups. It was thought that there were two reasons for the poor yield of this reaction. The first was the fact that lactams have been found, by Petasis,[96] to be less reactive to dimethyl titanocene reagent than other carbonyl compounds. Therefore, less of the target enamine was produced, this also explains the recovery of some starting material from the reaction mixture. It is also possible that the enamine is thermally unstable. Work involving the analogous glucose exoglycal (Section 2.9.2.1) suggested that this type of compound was thermally unstable; as a result it is possible that the enamine is even less stable and decomposes during the reaction.



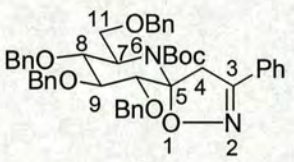
i) Cp_2TiMe_2; ii) PhClCNOH, NEt_3

Scheme 2.83

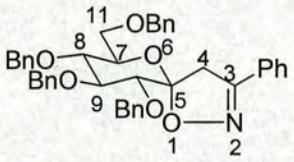
The above reaction was repeated on a larger scale; however, it was found not to be possible to isolate the enamine from the titanocene by-products. This was probably due to the ratio of dimethyl titanocene:lactam being increased from 2:1 to 3:1 in an effort to increase the yield of the reaction.

The final step of the reaction sequence was carried out using the crude enamine. The procedure used was identical to that employed for the pyranose analogues, where benzohydroximoyl chloride (**68**) and the crude enamine **60** were dissolved in sodium-dried ether and triethylamine in sodium-dried ether was added over 72 h. The work up yielded an oil. Column chromatography gave, in order of elution, an unidentified side product and a single isomer of the desired isoxazoline **187** as a white solid (35 mg, 3% over two steps), which was identified by ^{1}H NMR spectroscopy (Table 2.20) and mass spectrometry. The proton spectrum from a 360 MHz instrument gave a well resolved spectrum, from which the couplings were all determined. This spectrum indicated the presence of a single anomer, the NMR was also visually very similar to the analogous glucose derived spiroisoxazoline, the

corresponding pyranose analogue **133**. However, if it were assumed that the crude enamine reaction proceeded in the same yield as the test reaction it would be possible to estimate the yield for the cycloaddition reaction as being approximately 45%. Analysis by tlc indicated that a single anomer was present, the identity of which was determined by a NOESY experiment. The sample was irradiated at 3.12 ppm, the signal of the isoxazoline CH_2 group, and this resulted in an interaction at frequency of 3.75 ppm which corresponded with that of proton 10, as with the analogous oxygen containing compound in Section 2.10.3, this confirmed that the α-anomer had been synthesised.



187



133

Table 2.20: ^{1}H NMR data for **187**

Proton	δ_H/ppm	Coupling	*J*/Hz
4	3.12	7-8	9.8
7	4.08	7-11a	1.89
8	3.84	7-11b	2.9
9	4.15	8-9	9.5
10	3.75	9-10	9.7
11a	3.60	11a-11b	10.9

The limiting feature of this route was at the olefination stage, the enamine was a minor product the major product being an unidentified oil, which was not isolable from the enamine by crystallisation or chromatography. Further work is required to fully understand the processes present in this system.

2.15 Conclusions

The enamine *N*-Boc-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-6-aza-D-*gluco*-hept-1-enitol (**60**) was synthesised in a poor yield (8%) as a white crystalline solid using the olefination approach employing the Petasis reagent. This low yield was attributed to the low reactivity of the starting material and possible thermal instability of the product. It is

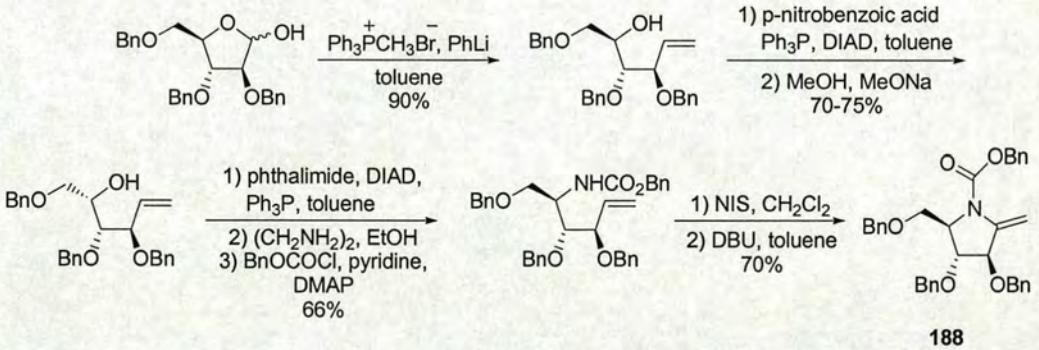
concluded that this is not the best method to this enamine. A more advantageous route would be to adapt the method proposed by Tatibouët *et al.*[138]

Benzonitrile oxide was cycloadded to *N*-Boc-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-6-aza-D-*gluco*-hept-1-enitol (**60**) to give a white solid identified as (5*R*,7*S*,8*R*,9*S*,10*R*)-*N*-Boc-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (**187**) as the α-anomer (3%, over two steps).

Although the above pyranosyl system was not very successful the work presented shows the potential for the cycloaddition of nitrile oxides to sugar enamines when considering the estimated yield of the cycloaddition step (45%) which could be optimised to give a useful approach to higher monosaccharides. A more reliable method for the production of those dipolarophiles is required.

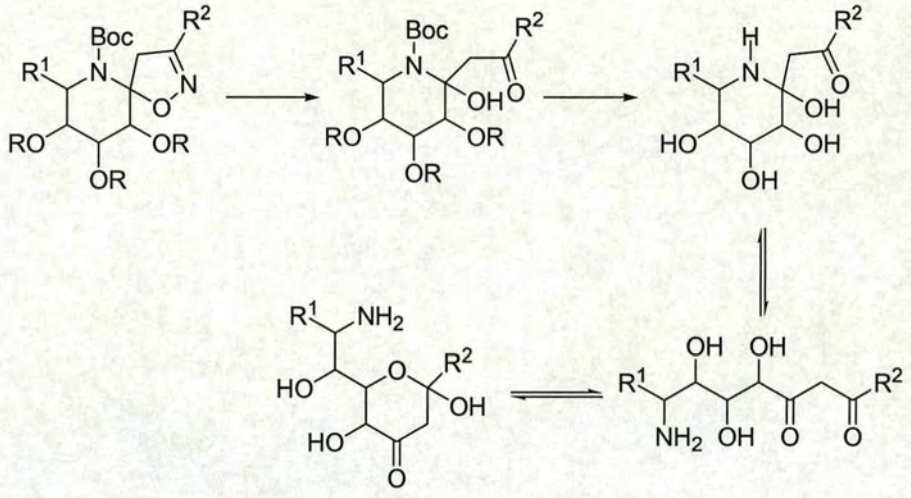
2.16 Future Work

Due to the problems discussed above with regard to the olefination of lactams it is felt that an alternative route to synthesise sugar derived enamines would be advantageous. To the best of this researcher's knowledge only one sugar-based enamine has been synthesised to date. Tatibouët *et al.*[138] produced an enamine (**188**) from D-arabinofuranose in 8 steps with moderate to good yields (Scheme 2.84).



Scheme 2.84

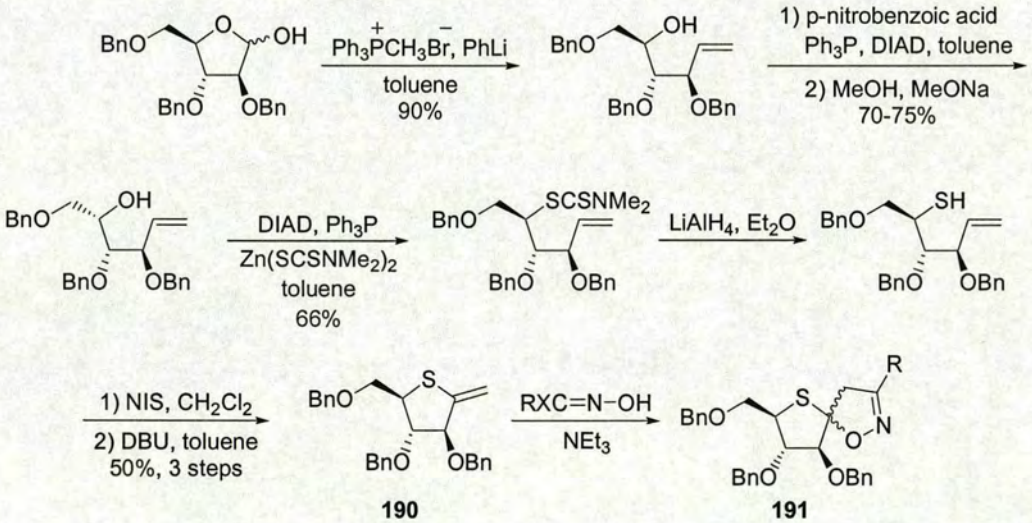
The immediate future for the azasugar work would be to obtain a stock of the enamine as produced by Tatibouët *et al*,[138] react it with benzonitrile oxide and carry out some pilot reductive ring opening reactions employing palladium hydroxide as the catalyst. A further aim would be to extend this work to other sugar systems or vary the nitrile oxides to allow access to a number of biologically active compounds **189** (Scheme 2.85) as discussed earlier.



189

Scheme 2.85

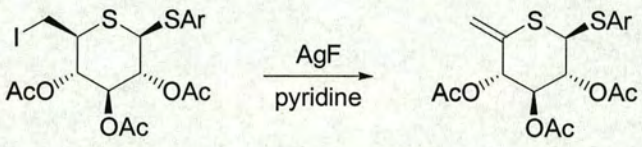
There has been some research into the potential of thiasugars as glycosidase inhibitors.[139] A D-arabinofuranose based heteroglycal **190** was synthesised by Tatibouët *et al*[138] in moderate to good yields over 7 steps (Scheme 2.86). It was felt that we could expand on this work by exploring the possibility of applying nitrile oxide cycloaddition chemistry to this thiaglycal that would give access to a wide variety of spiroisoxazolines **191** for further reaction. This is the only heteroglycal of its kind reported in the literature.



190 **191**

Scheme 2.86

Only one other thiasugar has been synthesised with an unsaturated bond directly attached *exo* to the ring. 4-Cyanophenyl 6-deoxy-1,5-dithio-β-D-*xylo*-hex-5-enopyranoside **192** was synthesised from the 6-iodo-glycoside **193** by dehydroiodonation with silver fluoride in pyridine (Scheme 2.87).[139a]

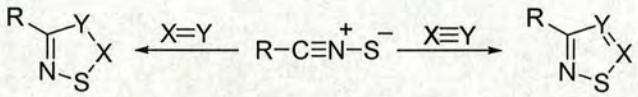


193 **192**

Scheme 2.87

2.17 Nitrile Sulfide Chemistry

Having explored applications of nitrile oxide chemistry in carbohydrate synthesis, it was decided to investigate the potential of nitrile sulfides for the preparation of pyranosyl-substituted heterocycles incorporating the C=N—S unit. Compared to other nitrilium betaines (nitrile oxides, nitrile ylides and nitrile imides)[3] nitrile sulfides have received relatively little coverage in the literature.[42,44] However, a variety of cycloadditions with double- and triple-bonded dipolarophiles have been reported (Scheme 2.88). These include alkenes, alkynes, nitriles, imines, carbonyl compounds, phosphaalkynes and thiocarbonyl compounds.



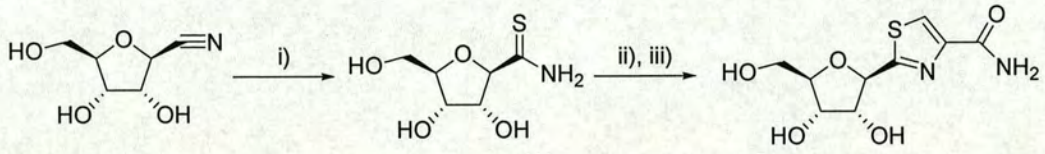
Scheme 2.88

A wide variety of substituents have been incorporated in the nitrile sulphide, including alkyl, aryl, heterocycles, phenols, esters and amides. There are few examples, however, of more complex nitrile sulfides such as carbohydrates. Rare examples are the furanosylnitrile sulfides reported by Buffel *et al.* as discussed in Section 1.7.8.[55,56] They showed that a number of target compounds (**46**, **47**, **48**, **49**) could be synthesised from a ribose based nitrile sulfide **45**. It was intended to apply Buffel's work to pyranose systems, rather than the furanose analogues employed previously.

The interest in this area comes from the enhanced biological stability of *C*-nucleosides which is due to their resistance to hydrolysis of the glycoside linkage, this is important with regard to anti-tumour activity.[55]

As discussed in section 1.7.8 pyrazofuran (**50**) is a good target for analogues as it has a range of anti-viral and anti-tumour activity and several analogues have already been produced.[55] Formycin A (**51a**) restricts the *de novo* purine synthesis,[140] has antineoplastic activity and as well as antifungal, antibacterial and antiviral activity.[55] While formycin B (**51b**) inhibits the purine nucleoside phosphorylase in human erythrocytes,[141] the growth of mouse sarcoma 180 cell and the influenza A_1 virus.[55]

Another ribose based anti-tumour agent is 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**194**).[56] This is an analogue of synthetic nucleoside ribovarin that was synthesised from nitrile **195** via thioamide **196** (Scheme 2.89).[142]

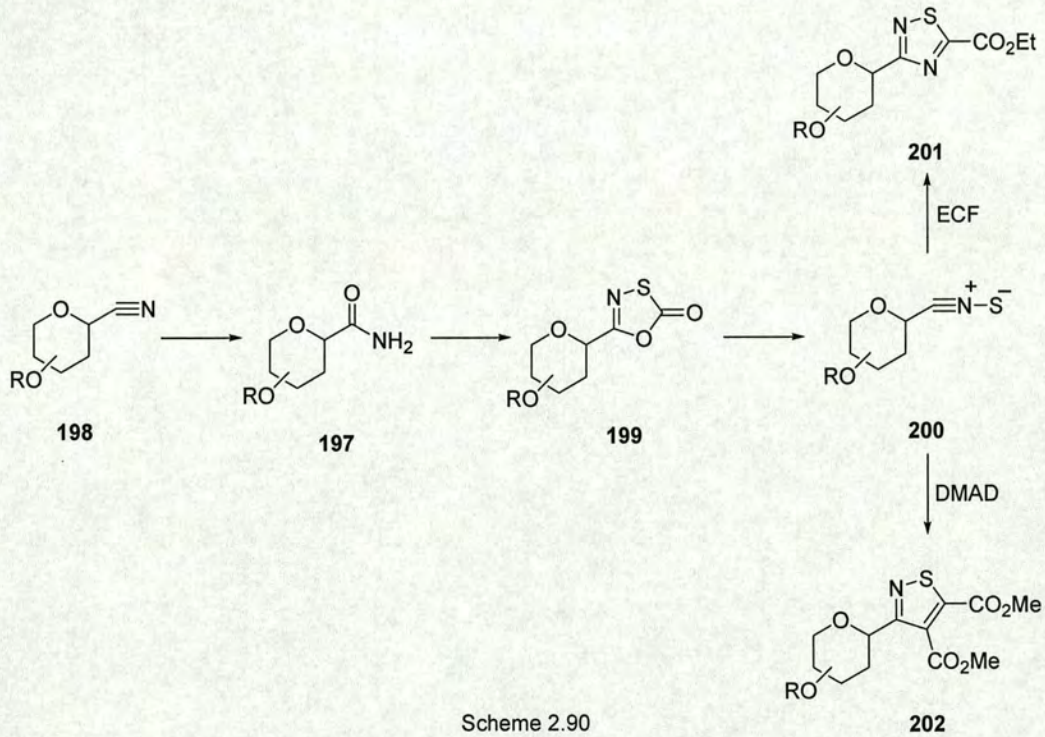


195 **196** **194**

i) H_2S, 4-dimethylaminopyridine; ii) $BrCH_2COCO_2C_2H_5$, AcCN; iii) NH_2, MeOH

Scheme 2.89

2.17.1 Nitrile Sulfide Precursors



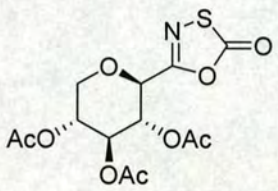
198 **197** **199** **200** **201** **202**

Scheme 2.90

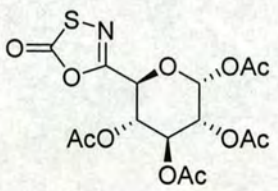
The most widely used method for the generation of nitrile sulfides is the thermal decarboxylation of the 5-substituted 1,3,4-oxathiazolones, which are usually prepared by reaction of chlorocarbonylsulfenyl chloride with the corresponding carboxamide. For the present research a route to pyranosyloxathiazolone **199** was therefore required. It was proposed that this could be achieved by hydrolysis of nitrile **198** to amide **197** and its

subsequent reaction with ClCOSCl (Scheme 2.90). The pyranosylnitrile sulfide **200** would then be generated by thermal decarboxylation of oxathiazolone **199** (Scheme 2.90) and trapped by reactions with ethyl cyanoformate and dimethyl acetylenedicarboxylate to afford novel *C*-glycosides **201** and **202**.

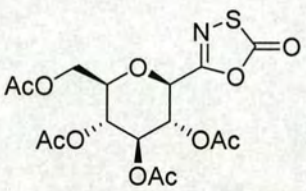
To demonstrate the feasibility of this chemistry three pyranosylnitrile sulfide precursors **203**, **204** and **205** were selected for the initial study, these were based on D-xylose and D-glucose. For **203** and **205** the nitrile sulphide would be attached to the anomeric position, whereas for **204** it would be at the non-reducing terminus C-5.



203

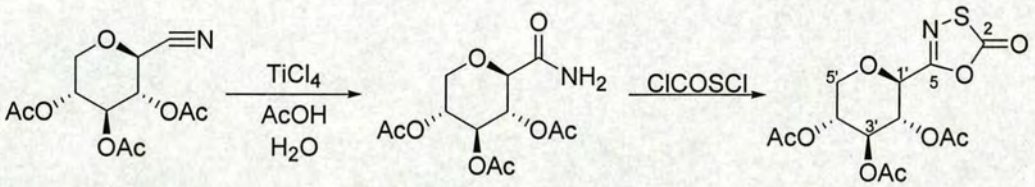


204



205

2.17.1.1 Synthesis of 5-(2',3',4'-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)-1,3,4-oxathiazol-2-one (203)



107 **206** **203**

Scheme 2.91

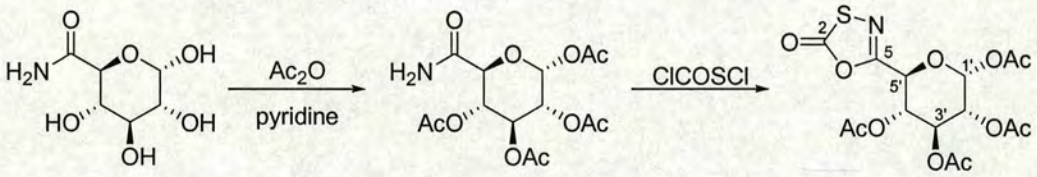
C-(2,3,4-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)formamide (**206**) was prepared from the xylose nitrile **107** described in Section 2.9.1. Following the method employed by BeMillar *et al.*,[143] titanium tetrachloride and water were added to a cooled suspension of the nitrile in glacial acetic acid (Scheme 2.91) and the reaction mixture allowed to stir for 72 h. Following extraction into chloroform and crystallisation, the product was obtained as a white solid (67%). The title oxathiazolone **203** was prepared using a modified method from Franz and Black.[40] The formamide **206** (1 eq.) from the previous step was dissolved in dry chloroform

with chlorocarbonylsulfenyl chloride (2.42 eq.) and the mixture was vigorously refluxed until the evolution of HCl ceased (48 h). Removal of the solvent and excess ClCOSCl, filtration and crystallisation yielded the title compound as a white solid (74%). The ^{13}C NMR spectrum showed characteristic peaks for the quaternary carbons of the oxathiazolone at 172.2 ppm and 155.4 ppm for C-2 and C-5, respectively (Table 2.21). The coupling constants (J 9-11 Hz) observed in the ^{1}H NMR spectrum for the sugar protons are characteristic of the sugar ring adopting a chair confromation.

Table 2.21: NMR data for **203**

Proton	δ_H/ppm	Coupling	J/Hz	Carbon	δ_C/ppm
1'	4.25	1'-2'	9.3	1', 2', 3', 4'	68.1, 69.1, 72.0, 74.5
2'	5.16	2'-3'	9.2	5'	66.8
3'	5.22	3'-4'	9.2	2	172.2
4'	5.00	4'-5a'	10.7	5	155.4
5a'	3.36	4'-5b'	5.5		
5b'	4.20	5a'-5b'	11.4		

2.17.1.2 Synthesis of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (204)



207 **204**

Scheme 2.92

C-(1,2,3,4-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5-yl)formamide (**207**) was produced by acetylation of commercially available glucuronamide (Scheme 2.92). Acetic anhydride was added to a solution of glucuronamide in pyridine and left to stir overnight. Concentration and crystallisation afforded the product **207** as white crystals (92%). The method employed for the conversion of amide **207** into oxathiazolone **204** was similar to that used in the synthesis of oxathiazolone **203** (Scheme 2.92). The formamide **207** was dissolved in dry toluene, chlorocarbonylsulfenyl chloride was added and the reaction mixture was heated at reflux for

6 h until the reaction was complete (tlc). Removal of the solvent and excess ClCOSCl and crystallisation from ethanol gave the title compound as white crystals (82%). As with oxathiazolone **203** the ^{13}C NMR spectrum showed characteristic peaks at 170.3 ppm for C- 2 and 155.4 ppm for C-5 of the oxathiazolone ring. The structure of the oxathiazolone ring was confirmed by x-ray crystal structure (Figure 2.18).

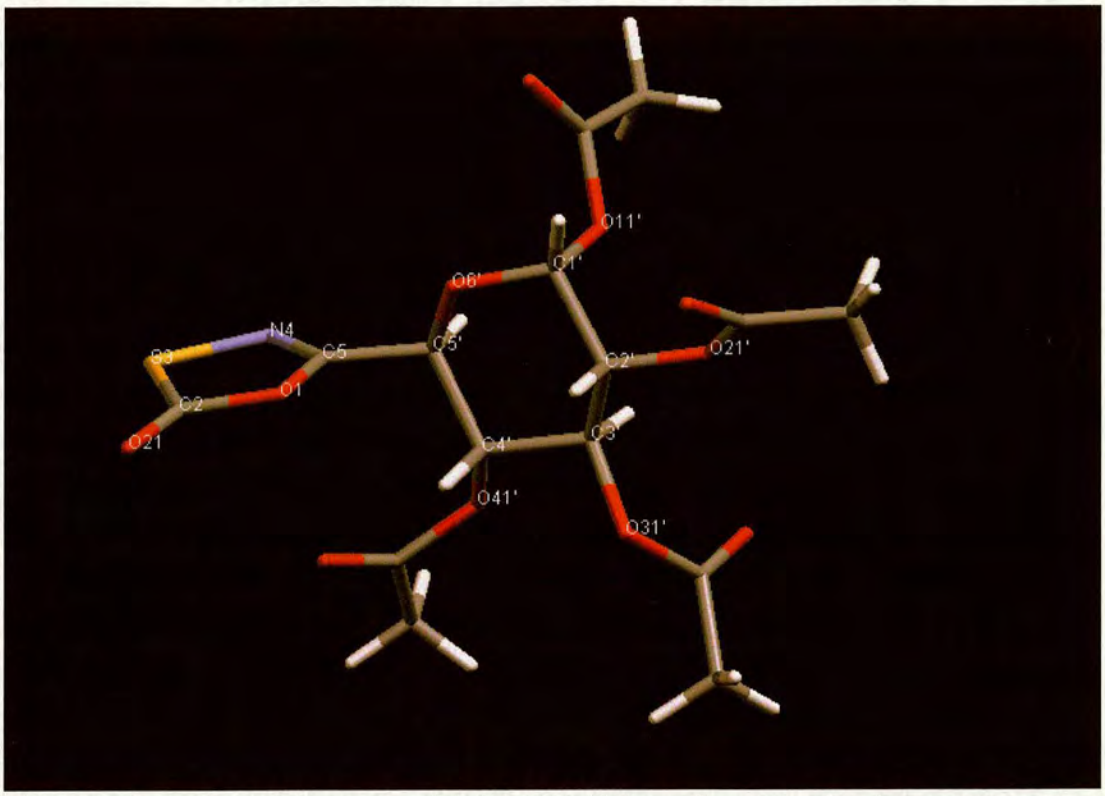


Figure 2.18: Crystal Structure of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (**204**); from a crystal produced by Mr M. Tackett.

The Haasnoot parameterisation of the Karplus equation[116] was employed to calculate the proton-proton coupling constants from the torsion angles taken from the crystal structure and compared to those found in the solution phase (Table 2.22). This gave a satisfactory correlation for the data presented, despite the substituents of the sugar ring as discussed for spiroisoxazolines **129** and **133** in Section 2.10.9.

Table 2.22: Calculated/Observed Coupling Constants

Protons	θ_{obs}/° [a]	J_{calc}/Hz [b]	J_{obs}/Hz
1',2'	+54.94	3.3	3.6
2',3'	-174.15	10.2	10.3
3',4'	+170.84	10.1	9.9
4',5'	-169.04	10.0	10.1

a. H-C-C-H Torsion Angle (θ) from x-ray data; b. $J_{calc}=7.76\cos^2\theta-1.1\cos\theta+1.4$

The Cremer and Pople puckering parameters[119] give an indication of the shape of the oxathiazolone and pyranose rings (Table 2.23). In this case the pyranose ring has 91% of the puckering of an ideal chair with Q = 0.577Å and θ = 4.4° compared to Q = 0.630Å and θ = 0° for an ideal chair. This value of θ indicated that the chair was in the $^4C_1$ conformation.

Table 2.23: Cremer and Pople Puckering Parameters

Ring		Q/Å	θ/°	ϕ/°
Pyranose	C(1')-C(2')-C(3')-C(4')-C(5')-O(6')	0.577	4.4	55.4
Oxathiazolone	O(1)-C(2)-S(3)-N(4)-C(5)	0.051		308.0

The oxathiazolone ring was found to be near planer with a mean deviation from plane of 0.0203Å (Table 2.24), while the ϕ value of 308.0° indicates a mainly twist conformation.

Table 2.24: Deviation of Oxathiazolone Ring from the Plane

Element	Deviation/Å
O(1)	+0.0323
C(2)	-0.0300
S(3)	+0.0185
N(4)	-0.0045
C(5)	-0.0164

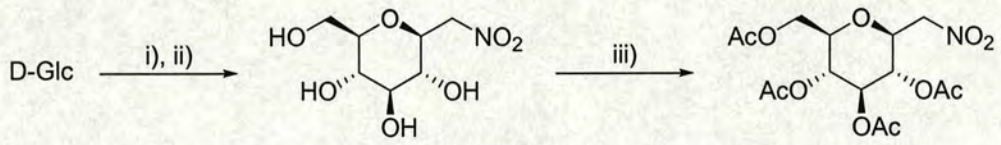
Table 2.25 shows the bond lengths and angles for the oxathiazolone ring, these were found to correspond favourably to the values for other, non-carbohydrate, oxathiazolones.[144]

Table 2.25: Bond Lengths and Angles of Oxathiazolone Ring in **204**

Bond	Length/Å	Atoms	Angle/°
O(1)-C(2)	1.383(3)	O(1)-C(5)-N(4)	120.6(23)
C(2)-O(21)	1.188(3)	C(5)-O(1)-C(2)	110.3(12)
C(2)-S(3)	1.753(3)	O(1)-C(2)-O(21)	122.8(21)
S(3)-N(4)	1.689(2)	O(1)-C(2)-S(3)	107.1(29)
N(4)-C(5)	1.262(3)	O(21)-C(2)-S(3)	130.1(8)
C(5)-O(1)	1.366(3)	C(2)-S(3)-N(4)	93.2(12)
C(5')-C(5)	1.495(3)	C(5)-N(4)-S(3)	108.6(26)

2.17.1.3 Synthesis of 5-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (205)

It was necessary to prepare the glucose nitrile **208** to allow the synthesis of oxathiazolone **205**. To this end glucopyranosylnitromethane **209** was prepared from D-glucose and the nitromethyl compound converted into nitrile **208**.



209

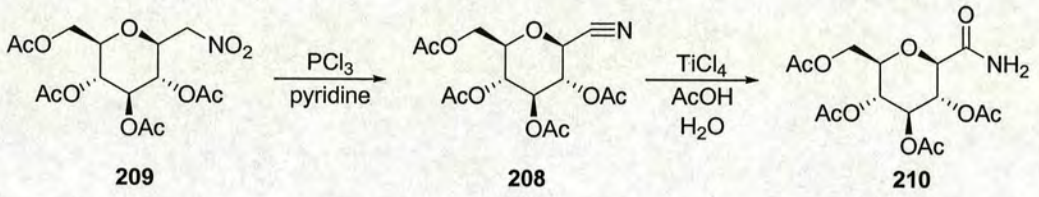
(i) NaOMe, CH_3NO_2, MeOH, (ii) H_2O, reflux, (iii) Ac_2O, TfOH

Scheme 2.93

The method used to produce 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl nitromethane (**209**) (Scheme 2.93) was similar to that employed for the xylose analogue **70**. Sodium methoxide solution was slowly added to a solution of D-glucose in methanol and nitromethane, the reaction mixture was left to stir, under nitrogen, overnight. The resulting solid was passed through an ion-exchange column, concentrated and carried on to the next stage without further purification.

The oil produced in the previous step was dissolved in water and heated at reflux overnight. The reaction mixture was filtered, extracted and concentrated to give the title compound as orange-brown crystals that were taken on to the next stage without further purification.

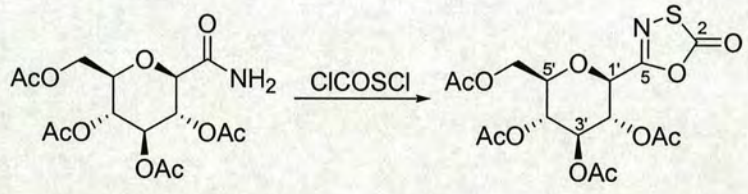
Triflic acid was added to a cold suspension of the crystals produced above in acetic anhydride, the reaction mixture was left to stir overnight. Ice-water was added and the reaction mixture underwent a series of extraction and heating steps that resulted in an oil which was crystallised to give glucopyranosyl nitromethane **209** as a white crystalline solid (13% over three steps).



209 **208** **210**

Scheme 2.94

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylnitrile (**208**) was prepared from acetylated nitromethyl glucose **209** (Scheme 2.94) using the same conditions employed for the xylose analogue **107**, as described in Section 2.9.1. This yielded the desired compound as a white crystalline solid (59%). The ^{13}C NMR showed a characteristic peak at 114.0 ppm for the quaternary C-1 of the nitrile functionality. Formamide **210** was produced using the same method as that employed for xylose formamide **206** in Section 2.17.1.1. This afforded *C*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)formamide (**210**) as fine white crystals (46%). The product was differentiated from nitrile **209** by the change in the C-1 frequency from 114 ppm to ~170 ppm.



210 **205**

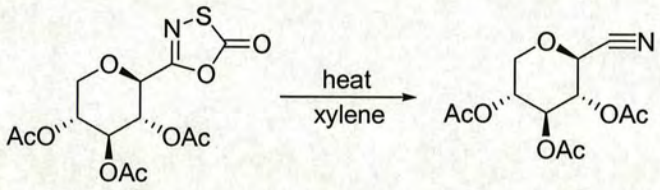
Scheme 2.95

The method used for the final stage (Scheme 2.95) was similar to those used in the previous oxathiazolone syntheses. The formamide **210** (1 eq.) produced in the above step was dissolved in dry toluene with chlorocarbonylsulfenyl chloride (4.5 eq.). The reaction mixture was heated at reflux for 4 h and work up yielded the title compound **205** as a white solid (75%). The ^{13}C NMR spectrum showed characteristic peaks for the quaternary carbons of the oxathiazolone at 170.0 ppm and 156.1 ppm for C-2 and C-5, respectively.

2.17.2 Reactions of Pyranosyl Oxathiazolones

Due to the competing reactions of cycloaddition and fragmentation for nitrile sulfides, as discussed in Section 1.7.7, it was decided to examine the decomposition time for the thermolysis of oxathiazolones prior to attempting any trapping reactions.

2.17.2.1 Decomposition of 5-(2',3',4'-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)-1,3,4-oxathiazol-2-one (203)

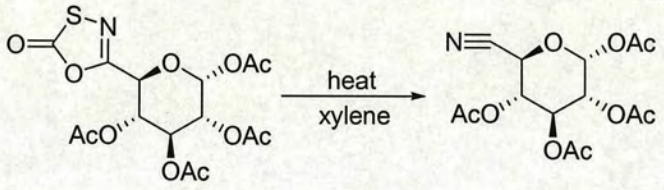


203 **107**

Scheme 2.96

The title compound **203** was dissolved in xylene and heated at reflux until all the starting material had been consumed (36h). Due to the similar tlc R_f values of nitrile **107** and oxathiazolone **203** this reaction was monitored by ^{1}H NMR spectroscopy. Once the reaction was complete the solvent was removed to leave nitrile **107** as a white solid (100%) (Scheme 2.96), which was identified by comparison with an authentic sample, as prepared in section 2.9.1. This reaction established the maximum heating time for the nitrile sulfide generation and trapping reactions.

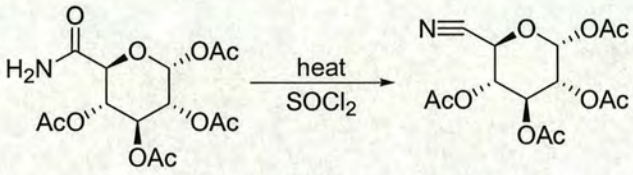
2.17.2.2 Decomposition of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (204)



204 **211**

Scheme 2.97

The title compound was dissolved in mesytilene and heated at reflux for 72 h. Work up yielded the expected decomposition product in the form of a white solid that was identified as nitrile **211** (100%) (Scheme 2.97). This decomposition reaction indicates the time taken for the oxathiazolone to degrade to the nitrile and, therefore, the maximum heating time required for the thermal trapping reaction.



207 **211**

Scheme 2.98

With a view to obtaining a pure sample of nitrile **211**, the parent amide **207** was refluxed in thionyl chloride to afford the title compound (74%) as a white solid (Scheme 2.98) that was identified by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. This reaction was carried out as literature data for this nitrile was not available to allow identification of the decomposition product prepared above.

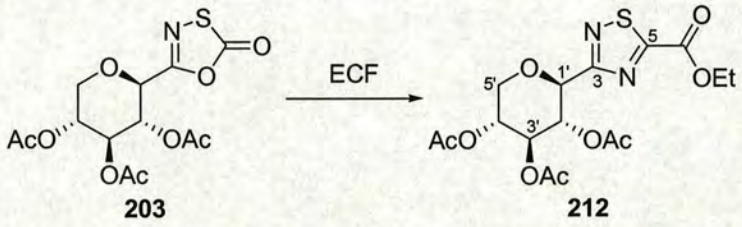
2.17.2.3 Attempted Reaction of 5-(2',3',4'-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)-1,3,4-oxathiazol-2-one (203) and Ethyl Cyanoformate (ECF)

Xylopyranosyl oxathiazolone **203** (100 mg) and ECF (9 eq.) were dissolved in xylene and heated at reflux for 72 h, under nitrogen. Work up yielded the starting oxathiazolone and the corresponding nitrile **107** as an unseparable mixture (38 mg) in a 1:1 ratio as identified from the ^{1}H NMR spectrum. Although none of the nitrile sulfide had been trapped, formation of the nitrile indicated that the nitrile sulfide had been generated.[41]

2.17.2.4 Attempted Reaction of 5-(2',3',4'-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)-1,3,4-oxathiazol-2-one (203) and Dimethyl Acetylenedicarboxylate (DMAD)

The method employed was similar to that used above. Oxathiazolone **203** (100 mg) and ECF (9 eq.) were dissolved in xylene and the reaction mixture was refluxed for 48 h. This reaction yielded only nitrile **107** (100%). There was no indication of the desired cycloadduct being present.

2.17.2.5 Synthesis of Ethyl 3-(2',3',4'-tri-*O*-acetyl-β-D-*xylo*-furanosyl)-1,2,4-thiadiazole-5-carboxylate (212)



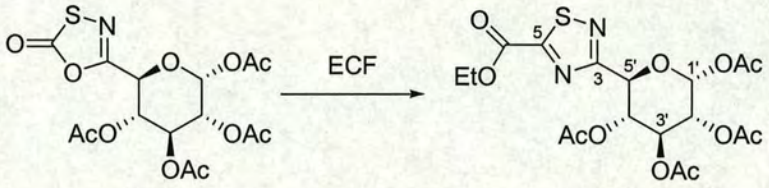
Scheme 2.99

Due to the lack of success in trapping the nitrile sulfide from oxathiazolone **203** using normal thermal methods it was decided to explore the use of microwave radiation. It was anticipated that this would allow shorter reaction times and it was hoped that the avoidance of prolonged thermolysis at elevated temperatures would give cleaner reaction mixtures.

Oxathiazolone **203** (100 mg) and ECF (17 eq.) were dissolved in mesitylene, the ramp time of the reaction was 10 min and the reaction mixture was irradiated for 5 min at 130°C (Scheme 2.99). Concentration of the reaction mixture and dry flash column chromatography gave the starting material **203** (48%), the nitrile **107** (8%), the amide **206** (7%) and a trace amount of the title compound. The quantity of the product was not sufficient to allow isolation and characterisation; however, the mass spectrum of the crude mixture contained a peak that was attributable to the product (M^++1 417). A surprising feature of this reaction was the formation of the amide as well as the usual nitrile decomposition product. This was probably due to the nitrile reacting with atmospheric water as these reactions were not carried out under a nitrogen atmosphere.

As there was a quantity of the oxathiazolone remaining after a 5 min irradiation it was decided to double the exposure time to 10 min in order to ensure the consumption of the starting material and perhaps allow the isolation of characterisable amount of the cycloadduct. As before oxthiazolone **203** (100 mg) and ECF (17 eq.) were dissolved in mesitylene and irradiated in the microwave reactor. When worked up it was found that all oxathiazolone **203** had been consumed, however the reaction mixture yielded only a trace amount of the product as well as nitrile (23%) and amide (32%) decomposition products that were isolated by filtration through a thin silica pad.

2.17.2.6 Synthesis of Ethyl 3-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (213): Method 1



204 **213**

Scheme 2.100

This experiment was carried out in collaboration with Mr M. Tackett.[145]

Oxathiazolone **204** (500 mg) and ethyl cyanoformate (17 eq.) were dissolved in mesitylene and the reaction mixture was heated at reflux for 24 h (Scheme 2.100). Concentration and column chromatography yielded nitrile **211** and the product **213** as a white solid. Preparative tlc resulted in the isolation of the title compound as a white solid (1%). The title compound was identified by the mass spectrum and by the proton NMR spectrum (Table 2.26). The latter exhibited a major change in the chemical shift of 5-H, in oxathiazolone **204** the signal for this proton was at 4.75 ppm while in the product it had been shifted to 5.37 ppm. As well as the sugar ring protons the NMR also showed signals attributable to the CH_2 and CH_3 of the ester group at 4.53 ppm and 1.46 ppm, respectively.

Table 2.26: ^{1}H NMR data for **213**

Proton	δ_H/ppm	Coupling	*J*/Hz
$\underline{CH_3}CH_2CO_2$	1.46	CH_3-CH_2	7.1
$CH_3\underline{CH_2}CO_2$	4.53	1'-2'	3.8
1'	6.49	2'-3'	10.4
2'	5.29	3'-4'	9.7
3'	5.67	4'-5'	9.8
4'	5.52		
5'	5.37		

2.17.2.7 Synthesis of Ethyl 3-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (213): Method 2

Oxathiazolone **204** (105 mg) and ECF (17 eq.) were dissolved in mesitylene and the reaction mixture irradiated in the microwave for 15 min at 130°C (Scheme 2.99). Work up gave a mixture (47 mg) of the starting material, the title compound and amide **207**. However, it was not possible to isolate the thiadiazole **213** from the starting material. The ^{1}H NMR spectrum showed that a small amount of the cycloadduct was present in the mixture, which was confirmed by FAB mass spectrometry.

2.17.2.8 Attempted Reaction of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (204) and Dimethyl Acetylenedicarboxylate

This experiment was carried out in collaboration with Mr M. Tackett.

Oxathiazolone **201** (500 mg) and DMAD (15 eq.) were dissolved in mesitylene and heated at reflux for 24 h. Work up resulted in the recovery of the starting material (61%) and the nitrile decomposition product **211** (25%).

2.17.2.9 Attempted Reaction of 5-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (205) and Ethyl Cyanoformate

Oxathiazolone **205** (148 mg) and ECF (17 eq.) were dissolved in mesitylene and the reaction mixture irradiated in a microwave for 15 min at 130°C. Work up yielded and inseparable mixture (84 mg) of the oxathiazolone **205**, amide **210** and the nitrile **208**. The ^{1}H NMR spectrum indicated that the oxathiazolone and the nitrile were present in approximately 1:1 ratio.

2.18 Conclusion

The work presented here has extended that of Buffel *et al*[55,56] to pyranosyl sugars. Three novel nitrile sulfide precursors were synthesised 5-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (**203**), 5-(1',2',3',4'-tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5-yl)-1,3,4-oxathiazol-2-one (**204**) and 5-(2',3',4',6'-tetra-*O*-acetyl-β-D-

glucopyranosyl)-1,3,4-oxathiazol-2-one (**205**). These were produced in good overall yields from their respective amides (**233**, 74%; **204**, 82%; **205**, 75%) as crystalline solids.

A variety of conditions were employed in experiments designed to generate and trap the nitrile sulfides. These experiments achieved mixed success. When heated in a microwave reactor for 10 min the xylopyranosyl oxathiazolone **203** gave traces of (~1%) of the cycloadduct ethyl 3-(2',3',4'-tri-*O*-acetyl-β-D-*xylo*-furanosyl)-1,2,4-thiadiazol-5-carboxylate (**211**), the major by-products being nitrile **107** and amide **206**. When oxathiazolone **203** was heated in refluxing xylene with ECF only the nitrile **107** was obtained. Heating the glucuronamide-derived oxathiazolone **204** in mesitylene with the dipolarophile resulted in a ethyl 3-(1',2',3',4'-tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,2,4-thiadiazol-5-carboxylate (**213**) in a poor yield (1%). When a similar reaction was carried out in a microwave reactor the oxathiazolone was recovered, although a small amount of cycloadduct **213** was identified in the ^{1}H NMR spectrum of the crude mixture. Heating glucopyranosyl oxathiazolone **205** in a microwave reactor produced a mixture of the oxathiazolone **205** and nitrile **208**. There was no evidence, in this case, to suggest that a cycloaddition had taken place.

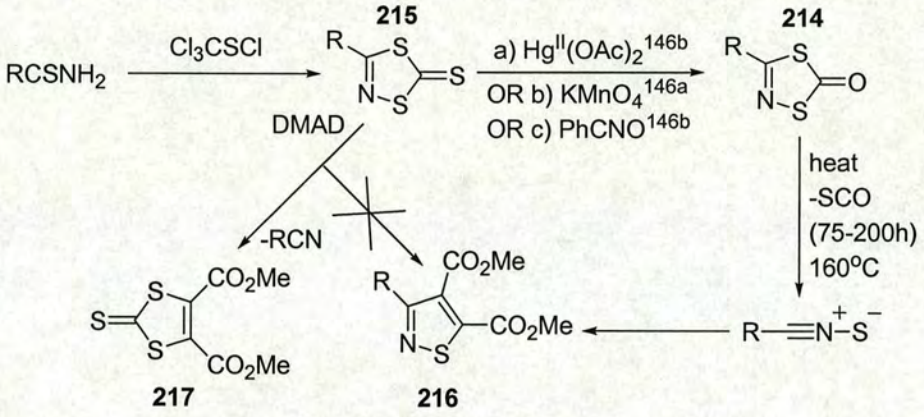
The production of nitriles **107** and **211** on heating of oxathiazolones **203** and **204**, in the absence of dipolarophile, is consistent with nitrile sulphide formation on thermolysis rather than the oxathiazolone decomposing via another route. The very low yields of cycloadducts indicates that the decomposition rate of pyranosylnitrile sulfides is greater than the rate of trapping by the dipolarophiles employed for this purpose.

The route described is a useful approach to sugar derived oxathiazolones. However, so far attempts to trap the nitrile sulfides in useful yields have not been successful, even with reactive dipolarophiles. Furthermore, problems have been encountered in separating cycloadducts from the oxathiazolone and the nitrile by product.

2.19 Alternative Routes to Nitrile Sulfides

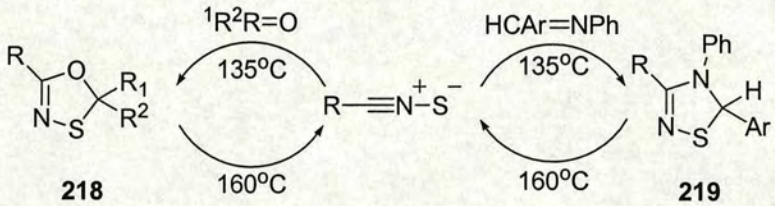
There are a number of alternative precursors to nitrile sulfides, these will be discussed below. The first (Scheme 2.101) is to use 1,4,2-diathiazol-5-ones (**214**)[146,147] and 5-thiones (**215**).[146a,148] The former fragments more slowly than oxathiazolones and affords isothiazoles (**216**) in good yields when heated in the presence of DMAD.[147] In contrast thione **214** reacts

directly with DMAD to afford dithiolethione (**217**), and no nitrile sulfide-derived products are observed.[148b] The access to these precursors is, however, less straight forward than to the oxathiazolones and the forcing conditions required to produce the nitrile sulfides would make the diathiazolone approach restrictive.



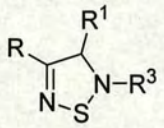
Scheme 2.101

Other potential routes are from 1,3,4-oxathiazoles (**218**)[149,150] and 4,5-dihydro-1,2,4-thiadiazoles (**219**),[151] both decompose slowly at high temperatures to give nitrile sulphide-derived products. However, there are few synthetic routes to these compounds short of reacting the target nitrile sulfide with the relevant unsaturated system (Scheme 2.102),[42] thus negating this as a useful synthetic technique. Furthermore, the conditions required to generate the nitrile sulphides are highly forcing and the reported yields are low.



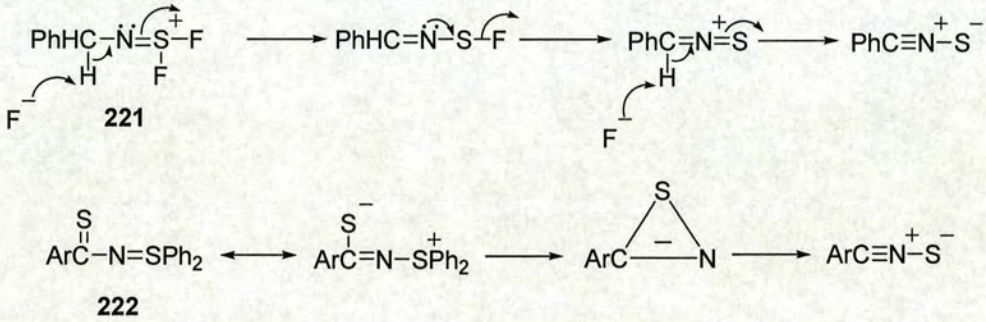
Scheme 2.102

It has also been attempted to produce nitrile sulfides by the thermolysis of a number of 1,2,5-thiadiazoles (**220**), however this resulted in decomposition directly to the corresponding nitrile and sulphur.[60]



220

Finally (Scheme 2.103), nitrile sulfides have also been generated by the thermolysis of (alkylimino) sulphur difluorides (**221**)[62,152] and N-thioacyldiphenylsulphinimides (**222**).[153] These were found to be of limited synthetic use.



Scheme 2.103

2.20 Future Work

It may be possible to improve the generation and trapping of nitrile sulfides by exploring other solvents used in conjunction with the microwave conditions. For example, subsequent work in the group showed that lower boiling solvents will allow for easier work up of reactions, but allows the reaction to proceed at a temperature higher than that of the solvent's boiling point.[154] More polar solvents, e.g. 1,2-dichloroethane may improve the heating of the reaction mixture. The sugar based oxathiazolones may also have potential as water-soluble oxathiazolone fungicides. This would require the protection strategy to be altered from an ester group to an ether group to allow the deprotection of the sugar ring without the degradation of the oxathiazolone moiety through nucleophilic attack. There is also the possibility of using oxathiazolone reaction products as ligands in transition metal chemistry,[65] therefore these compounds may have a future as chiral ligands.

3. Experimental

3.1 General

3.1.1 Instrumentation

Melting points were measured on a Gallenkamp capillary tube apparatus and are uncorrected.

All ^{1}H and ^{13}C NMR were recorded on Bruker AX250 and WP200SY instruments by Mr J. R. A. Millar and Mr W. Kerr. Chemical Shifts (δ) in all spectra are measured in parts per million using tetramethylsilane (δ = 0.0) as a reference signal.

FAB mass spectra and exact mass measurements were recorded on a Kratos MS50TC instrument using either glycerol or thioglycerol as matrix by Mr A. Taylor and Mr H. M^{c}Kenzie.

The x-ray structural analysis was carried out by Dr A. Dawson, Dr A. Parkin and Dr S. Parsons.

Infrared spectra were recorded on a Jasco FT/IR-460 Plus using sodium chloride plates.

The microwave experiments were carried out using CEM Explorer microwave system controlled by Discover software.

3.1.2 Chromatography

Analytical tlc was carried out on Polygram plastic-backed plates coated with silica gel (0.2 mm) with fluorescent indicator UV_{254} and Merck aluminium backed plates with Kieselgel GF_{254} (0.2 mm).

Dry flash chromatography was performed using sinters of 30mm diameter filled with Fluka Kiesegel GF_{254} silica and eluted under a vacuum supplied by a water pump.

3.1.3 Solvents and Reagents

All reagents were standard laboratory grade and were used as supplied, unless specifically stated in the text.

Dry ether, toluene and benzene were Analar grade dried over sodium wire.

Dry chloroform was obtained by distillation over calcium chloride and stored over 4Å molecular sieves.

Dry pyridine was Analar grade distilled from and stored over potassium hydroxide.

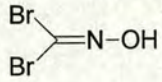
Dry THF was freshly distilled from calcium hydride.

Acetic anhydride was purified by fractional distillation and stored over 4Å molecular sieves.

3.2 Synthesis of Nitrile Oxide Precursors

3.2.1 Dibromoformaldoxime (66)[71,72]

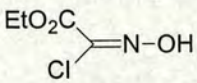
Lab. Book Ref. KG 5
Molecular Formula $CHBr_2NO$
Formula Weight 203



Hydroxylamine hydrochloride (7.44 g, 0.11 mol) was added to a stirred solution of glyoxylic acid (15.55 g, 50% w/w acid/water, 0.11 mol) and the resulting solution stirred for 24 hours at room temperature. Sodium carbonate (18.38 g, 0.17 mol) was cautiously added to the resulting suspension, this was followed by dichloromethane (100 ml). The resulting biphasic system was cooled to ~6°C using an ice bath. Bromine (23.39 g, 0.15 mol) in dichloromethane (50 ml) was added, with vigorous stirring. The addition was carried out at a rate such that the temperature never exceeded 10°C. The reaction mixture was stirred for three hours, after which the organic phase was separated from the aqueous; this was washed with dichloromethane (3 x 50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was recrystallised from n-hexane to yield a white crystalline solid (21.32 g, 29%); mp 69–70°C (lit.[18] 70-71°C).

3.2.2 Ethyl Chlorooximidoacetate (67)[73]

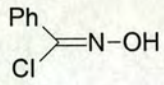
Lab. Book Ref. KG 7
Molecular Formula $C_4H_6ClNO_3$
Formula Weight 151.5



Glycine ethyl ester hydrochloride (30.13 g, 0.22 mol) was dissolved in distilled water (90 ml) and the solution was cooled, using a dry ice/acetone bath, to –20°C. Hydrochloric acid (18 ml, 37% w/w, 0.6 mol) was next added; followed, in a dropwise fashion, by a solution of sodium nitrite (14.52 g, 0.17 mol) in water (25 ml), at such at rate that the temperature of the reaction mixture did not exceed –20°C. The additions of HCl and $NaNO_2$ were repeated and the cooled suspension was stirred for 90 mins. The resulting solid was filtered off, washed with petroleum ether (40-60, 3 x 10 ml) and dried to afford the product (12.83 g, 39%) as white crystalline solid; mp 74-75°C (lit.[155] 79-80°C).

3.2.3 Benzohydroximoyl Chloride (68)[74]

Lab. Book Ref. KG 10
Molecular Formula $C_7H_6ClNO_3$
Formula Weight 155.5

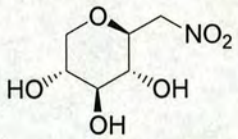


A solution of α-benzaldoxime (2.0 g, 0.12 mol) in dry chloroform (50 ml) was cooled to –10°C (dry ice/acetone bath). Chlorine gas was passed through the solution until the colour changed from Oxford blue to sunset yellow having passed through emerald green. The excess chlorine was removed by displacement with nitrogen gas. The solution was evaporated to dryness and the resulting white solid was recrystallised from pentane to yield the product as white prisms (1.77 g, 69%); mp 49-50°C (lit.[74] 50-51°C).[a]

3.2.4 Synthesis of 2,6-Anyhydro-3,4,5-tri-*O*-acetyl-1-chloro-1-deoxy-1-hydroxyimino-D-*glycero*-β-D-*xylo*-hexitol (72)

3.2.4.1 2,6-Anhydro-1-deoxy-1-nitro-D-*gulo*-heptitol (β-D-xylopyranosylnitromethane) (69)[76]

Lab. Book Ref. KG 66
Molecular Formula $C_6H_{11}NO_6$
Formula Weight 193



Sodium methoxide (2.68 g sodium in 88 ml methanol) was added, over 10 min, to a stirred suspension of xylose (9.12 g, 0.06 mol), nitromethane (45 ml, 50.7 g, 0.83 mol) and dry methanol (35 ml). This mixture was stirred overnight to give a brown solid, which was filtered off and dried by suction, washed with ice-cold methanol and again dried by suction. The solid was quickly dissolved in ice-cold water and passed down a column of amberlite IR 120 (plus) resin (~300 g).

To prepare the column water was passed through the column until the colour was lost. Then 1M HCl (100 ml) was added, after which more water was added until pH 4 was obtained. Once the solution prepared above had been passed through, the column was washed with

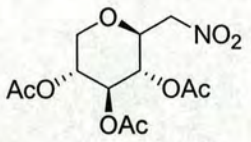
[a] The chlorine gas was generated by the addition of 30 ml of concentrated hydrochloric acid to 6 g of potassium permanganate.

water (100 ml) and the combined elutants were reduced *in vacuo* until only water distilled over.

The resulting mixture was refluxed overnight. Activated charcoal (5 g) was added and the solution was refluxed for a further 2 h, the reaction mixture was hot-filtered through a celite pad and the yellow solution was evaporated *in vacuo* to give a yellow oil that was carried on to the next step without further purification.

3.2.4.2 2,6-Anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-nitro-D-*gulo*-hepitol (3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane) (70)[75]

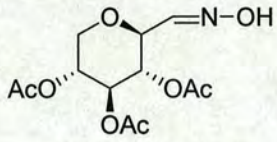
Lab. Book Ref. KG 69
Molecular Formula $C_{12}H_{17}NO_9$
Formula Weight 319



A suspension of 2,6-anhydro-1-deoxy-1-nitromethylxylose **69** in acetic anhydride (20 ml) was cooled to 0°C (ice bath) and stirred under a nitrogen atmosphere. Trifluoromethane sulphonic acid (0.1 ml) was added and the sugar slowly dissolved. The solution was stirred overnight while warming to room temperature, this was followed by addition of ice-water (100 ml). After stirring, the mixture was extracted with chloroform (2 x 100 ml); the organics were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the oil obtained co-evaporated with toluene (5 x 75 ml). The crude oil was dissolved in chloroform (100 ml) and stirred with activated charcoal (2 g) for 30 min. The solution was filtered through a celite pad and the solvent was removed to give the crude acetylated nitromethyl xylose. This was further co-evaporated with toluene and recrystallised from ethanol to give the title compound as a white solid (10.70 g, 37%); mp 163-164°C (lit.[156] 164-165°C); δ_H (250 MHz, $CDCl_3$) 2.30, 2.33 (9H, 3 x s, CH_3), 3.61 (1H, dd, 6a-H), 4.40 (1H, dd, 6b-H), 4.44 (1H, ddd, 2-H), 4.67 (1H, dd, 1b-H), 4.76 (1H, dd, 1a-H), 5.15 (1H, dd, 3-H), 5.26 (1H, dd, 5-H), 5.52 (1H, t, 4-H); *J*(x-y)/Hz 1a-1b 13.4, 1a-2 8.9, 1b-2 3.0, 2-3 10.1, 3-4 9.3, 4-5 9.4, 5-6a 5.7, 5-6b 10.6, 6a-6b 11.4; δ_C (63 MHz, $CDCl_3$) 21.0, 21.0, 21.2 (3 x $COCH_3$), 67.1 (C-6), 69.0, 69.9, 73.5, 75.4 (C-2, C-3, C-4, C-5), 76.4 (C-1), 170.2, 170.2, 170.6 (3 x $COCH_3$).

3.2.4.3 2,6-Anyhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-hydroxyimino-D-*glycero*-β-D-*xylo*-hexitol (71)[77]

Lab. Book Ref. KG 143
Molecular Formula $C_{12}H_{17}NO_8$
Formula Weight 303

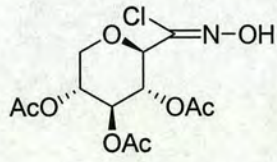


The Baker *et al*[76] modified method from Bartra *et al*,[77] was employed to reduce the acetylated nitromethyl xylose **70** to the oxime.

Tin (IV) chloride (454 mg, 0.21 mol, 1.5 eq) was dissolved, under nitrogen, in dry THF (6 ml) and was cooled to 0°C. Triethylamine (1.09 ml, 7.76 mmol, 5 eq) and thiophenol (0.73 ml, 7.07 mmol, 4.5 eq) were then added to give a yellow mixture. The acetylated nitromethyl xylose **70** (501 mg, 1.57 mmol, 1 eq) dissolved in dry THF (6 ml) was added dropwise to the reaction mixture, which was left to stir overnight while allowing to warm to room temperature. The solvent was removed *in vacuo* to give a yellow solid that was co-evaporated with hexane (3 x 50 ml). The solid was purified using column chromatography (silica, 0 →100% ether in hexane; gradient elution) to give the title compound as a white crystalline solid (309 mg, 65%); mp 130°C (lit.[76] 135-137°C; lit.[157] 160-163°C); R_f 0.50 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.87, 1.93, 1.93 (9H, 3 x s, CH_3), 3.25 (1H, t, 6a-H), 3.88 (1H, dd, 2-H), 4.04 (1H, dd, 6b-H), 4.70 (1H, broad s, OH), 4.90 (1H, ddd, 5-H), 4.94 (1H, t, 3-H), 5.15 (1H, t, 4-H), 7.19 (1H, d, 1-H); *J*(x-y)/Hz 1-2 6.7, 2-3 9.8, 3-4 9.5, 4-5 9.4, 5-6a 10.9, 5-6b 5.6, 6a-6b 11.3; δ_C (63 MHz, $CDCl_3$) 20.7, 20.8 (3 x CH_3), 66.7 (C-6), 69.0, 69.9, 72.8 (C-3, C-4, C-5), 76.2 (C-2), 146.8 (C-1), 170.0, 170.1, 170.6 (3 x $COCH_3$); *m/z*(FAB) Found: M^++1 304.1026. $C_{12}H_{18}NO_8$ requires M^++1 304.1032.

3.2.4.4 2,6-Anyhydro-3,4,5-tri-*O*-acetyl-1-chloro-1-deoxy-1-hydroxyimino-D-*glycero*-β-D-*xylo*-hexitol (72)[74]

Lab. Book Ref. KG 220
Molecular Formula $C_{12}H_{16}ClNO_8$
Formula Weight 337.5



A solution of the above oxime **71** (234 mg, 0.77 mmol) in dry chloroform (25 ml) was cooled to –78°C (dry ice/acetone bath). Dry chlorine gas was slowly bubbled through the

solution until the solution became a green colour having first passed through blue. The reaction mixture was allowed to warm overnight with stirring during which time the colour faded. The solvent was removed *in vacuo* to give an oil that was triturated from ether to give the title compound as a white solid (260 mg, 100 %); mp 140-141°C; δ_H (250 MHz, $CDCl_3$) 2.18, 2.23, 2.24 (9H, 3 x s, CH_3), 3.60 (1H, t, 6a-H), 4.36-4.49 (2H, m, 2-H, 6b-H), 5.21-5.31 (1H, m, 5-H), 5.36-5.54 (2H, m, 3-H, 4-H), 9.40 (1H, broad s, OH); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5 nd, 5-6a 10.8, 5-6b nd, 6a-6b 10.8; δ_C (63 MHz, $CDCl_3$) 20.4 x 2, 20.5 (3 x CH_3), 66.5 (C-6), 68.5, 68.9, 73.2, 78.8 (C-2, C-3, C-4, C-5), 136.2 (C-1), 169.3, 169.9, 170.5 (3 x $COCH_3$); *m/z*(FAB) Found: M^++1 338.0643. $C_{12}H_{17}NO_8Cl$ requires M^++1 338.0644.

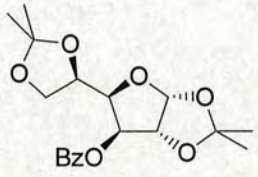
3.3 Synthesis of Hex-5-enofuranosides

3.3.1 Synthesis of 3-*O*-Benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (58)

The title compound was synthesised in four steps from commercially available diacetone-D-glucose, as previously reported.[78]

3.3.1.1 3-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (75)

Lab. Book Ref. KG 1
Molecular Formula $C_{19}H_{24}O_7$
Formula Weight 336



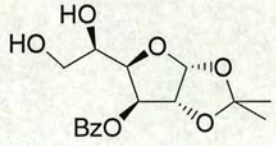
Diacetone-D-glucose (20.57 g, 79.0 mmol) was dissolved in chloroform (50 ml) under nitrogen, and pyridine (80 ml) was added. Then, using an ice bath, the solution was cooled to 0°C and benzoyl chloride (16 ml, 138 mmol) added in a dropwise fashion. The solution was then stirred overnight. The resulting green solution was, poured slowly into water (250 ml), the aqueous layer separated and extracted with chloroform (2 x 50 ml). The combined organic layers were washed with saturated aq. $NaHCO_3$ (3 x 75 ml) and water (2 x 75 ml). The combined organic layers were then dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the product as an oil, that was not purified, but taken directly on to the next stage.

3.3.1.2 3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (76)

Lab. Book Ref. KG 2

Molecular Formula $C_{16}H_{20}O_7$

Formula Weight 324



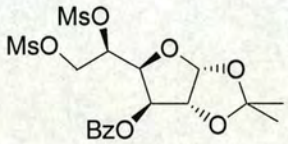
The benzoylated-D-glucose **75** produced in the previous step was stirred overnight at 40°C with glacial acetic acid (100 ml) and water (60 ml). The resulting solution was added to chloroform/water (1:1, 400 ml), and the aqueous layer extracted with chloroform (2 x 100 ml). The combined organic layers were then washed with H_2O (200 ml) before being dried ($MgSO_4$). The organic layers were co-evaporated with toluene to give an oil, which was carried forward to the next stage.

3.3.1.3 3-*O*-Benzoyl-1,2-*O*-isopropylidene-5,6-bis-*O*-methanesulphonyl-α-D-glucofuranose (77)

Lab. Book Ref. KG 3

Molecular Formula $C_{18}H_{24}O_{11}S_2$

Formula Weight 480



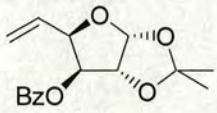
The oil produced in the above step was dissolved, under nitrogen, in 100 ml dry chloroform, to which pyridine (50 ml) was added. The solution was cooled (salt-ice bath), and methanesulphonyl chloride (22.05 g, 0.19 mol) was added dropwise to the reaction mixture, which was then allowed to return to room temperature, and stirred overnight. The resulting suspension was poured into chloroform/water (1:1, 300 ml) and the aqueous phase extracted with chloroform (2 x 100 ml). The combined organic layers were next washed with 1M H_2SO_4 (3 x 100 ml), sat. $NaHCO_3$ (2 x 100 ml) and water (2 x 100 ml). The solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil that gave crystals on the addition of ethanol. The product was recrystallised from ethanol (10.61 g, 28% from **74**); mp 168-169°C (lit.[79] 168-169°C).

3.3.1.4 3-*O*-Benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (58)[80]

Lab. Book Ref. KG 4

Molecular Formula $C_{16}H_{19}O_5$

Formula Weight 273



Prior to production of the alkene a zinc/copper couple had to be prepared. This was achieved by thoroughly washing powdered zinc (3.44 g) with 1M HCl (4 x 15 ml), water (2 x 15 ml), $CuSO_4$ (3 x 15 ml), water (2 x 15 ml), ethanol (2 x 15 ml) and DMF (3 x 15 ml).

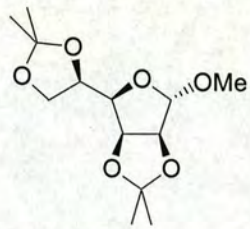
The freshly prepared Zn/Cu couple was added to a stirred solution of 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-5,6-bis-*O*-methanesulphonyl-α-D-glucofuranose (**77**) (4.77 g, 9.93 mmol), dry sodium iodide (7.50 g, 0.05 mol), DMF (20 ml) and DME (6 ml). The resulting mixture was then refluxed for 70 mins. The solution was allowed to cool, after which it was poured into water (200 ml) and toluene (150 ml) added. The mixture was then filtered through a celite pad and the pad was washed with toluene (2 x 100 ml). The washings were then used to extract the aqueous layer; the combined organics were next washed with water (2 x 100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was recrystallised from petroleum ether (60-80) and washed with n-pentane to afford the product as a white solid (2.22 g, 77%); mp 70°C; $[\alpha]_D^{18}$ –57.0 (c = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.32, 1.55 (6H, 2 x s, $C(CH_3)_2$), 4.68 (1H, dd, 2-H), 4.85 (1H, dd, 4-H), 5.23-5.28 (2H, m, 6a-H, 6b-H), 5.44 (1H, d, 3-H), 5.80-5.94 (1H, dm, 5-H), 6.02 (1H, d, 1-H), 7.25-8.02 (5H, m, Ph); *J*(x-y)/Hz 1-2 3.8, 2-3 3.0, 3-4 3.0, 4-5 6.4, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 26.0, 26.5 ($C(CH_3)_2$) 77.7, 80.1 (C-3, C-4), 83.4 (C-2), 104.5 (C-1), 1 11.9 ($C(CH_3)_2$), 1 19.5 (C-6), 1 28.3 (2 x CHPh), 1 29.17 (qCPh), 129.54 (2 x CHPh), 130.5 (C-5), 133.3 (CHPh), 165.1 (*C*OPh); *m/z*(FAB) Found: M^++1 291.1230. $C_{16}H_{19}O_5$ requires M^++1 291.1233.

3.3.2 Synthesis of Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-eno furanoside (61)

The title compound was prepared using a literature procedure.[81]

3.3.2.1 Methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (78)

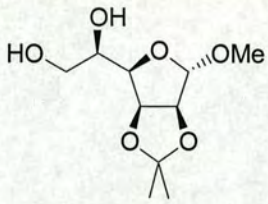
Lab. Book Ref. KG 70
Molecular Formula $C_{13}H_{22}O_6$
Formula Weight 274



A solution of D-mannose (25 g, 0.14 mol), 2,2-dimethoxypropane (85 ml), acetone (82.5 ml), methanol (82.5 ml) and concentrated hydrochloric acid (2.5 ml) was heated at reflux for 2 hr. The solution was cooled, water (250 ml) added and concentrated *in vacuo* to ~250 ml below 30°C. The product was not isolated but taken directly on to the next stage.

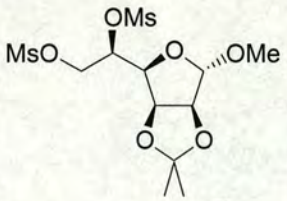
3.3.2.2 Methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (79)

Lab. Book Ref. KG 71
Molecular formula $C_{10}H_{18}O_6$
Formula Weight 234



To a stirred solution of furanoside **78**, prepared above, methanol (250 ml) and concentrated hydrochloric acid (6.25 ml) were added and the resulting solution stirred for 200 min. The solution was then neutralised by addition of sodium hydrogen carbonate solution (1M, 188 ml), the methanol was removed *in vacuo*. The compound was isolated in chloroform by liquid-liquid extraction for 3 hr. The extract was dried ($MgSO_4$) and then concentrated to afford a syrup, which was carried directly through to the next stage.

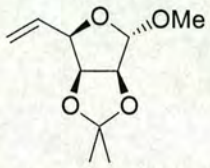
3.3.2.3 Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-mannofuranoside (80)



Lab. Book Ref. KG 72
Molecular Formula $C_{12}H_{22}O_{10}S_2$
Formula Weight 390

Syrup **79** was dissolved in pyridine (125 ml) and methanesulphonyl chloride (37.5 ml) added while maintaining the stirred solution below 35°C. The solution was stirred at 20°C for 3 hr, and the excess methanesulphonyl chloride was decomposed by slow addition of water, while keeping the temperature below 50°C. More water (~1500 ml) was added and the product was filtered off, washed with water and dried *in vacuo* over phosphorous pentoxide. The crude product was recrystallised from ethanol to yield white crystals (16.8g, 31% from D-mannose) that were taken on to the next stage.

3.3.2.4 Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-eno furanoside (61)[80]



Lab. Book Ref. KG 13
Molecular Formula $C_{10}H_{16}O_4$
Formula Weight 200

Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-*lyxo*-hex-5-enofuranoside (**80**) (5.03 g, 12.9 mmol) was dissolved in DMF (33 ml) and DME (9 ml) with dry sodium iodide (9.66 g, 0.06 mol). A freshly prepared Zn/Cu couple was added to the above mixture, which was refluxed for 70 min with stirring. The resulting solution was cooled and poured into water, with rapid stirring. Toluene (53 ml) was added and the mixture was filtered through a celite pad that was washed with toluene (2 x 83 ml). The filtrate was used to extract the aqueous layer of the reaction mixture; the combined organics were washed with water (2 x 50 ml) and evaporated *in vacuo* to give a yellow oil. The oil was purified by dry flash chromatography (hexane:ether 90:10) to give the pure alkene (1.98 g, 77%); δ_H (250 MHz, $CDCl_3$) 1.27, 1.43 (6H, 2 x s, $C(CH_3)_2$), 3.31 (1H, s, OMe), 4.35 (1H, dd, $J_{3,4}$ 3.6 $J_{4,5}$ 7.4, 4-H), 4.54 (1H, d, $J_{2,3}$ 5.8, 2-H), 4.64 (1H, dd, $J_{3,4}$ 3.6 $J_{2,3}$ 5.9, 3-H), 4.87 (1H, s, 1-H), 5.96, 5.87-6.04 (1H, ddd, $J_{4,5}$ 7.3 $J_{5,6a}$ nd J_{5-6b} nd, 5-H), 5.26-5.42 (2H, m, 6a-H, 6a-H); *J*(x-y)/Hz 1-2 ~0, 2-3 5.9, 3-4 3.6, 4-5 7.4, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 24.8,

25.9 (C(CH_3)$_2$) 54.6 (OMe), 81.0, 81.4 (C-2, C-3), 85.2 (C-4), 107.0 (C-1), 112.5 (*C*(CH_3)$_2$), 119.0 (C-6), 132.2 (C-5); *m/z*(FAB) Found: M^++1 201.1134. $C_{10}H_{17}O_4$ requires M^++1 201.1127.

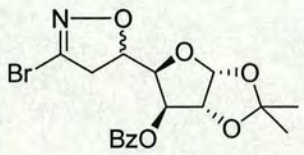
3.4 Cycloaddition Reactions of Hex-5-enofuranosides

3.4.1 General Method for Cycloaddition of Nitrile Oxides to Hex-5-enofuranosides[12,13]

The hex-5-enofuranoside (1.2 eq.) was dissolved in sodium-dried ether and the nitrile oxide precursor (1 eq.) added with stirring. The solution was cooled (ice bath) and triethylamine (1.2 eq.) in sodium-dried ether was added to the mixture over 48-72 h using a syringe pump. The solution was then stirred for a further ten hours, after which the triethylamine hydrochloride precipitate was dissolved by the addition of water. The aqueous layer was then extracted with ether, the combined organics were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The diasteromeric isoxazolines were separated from the unreacted alkene and the furoxan by dry flash column chromatography (silica, 0→100% diethyl ether in hexane; gradient elution).

3.4.2 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-bromo-2-isoxazoline (81)

Lab. Book Ref. KG 6
Molecular Formula $C_{17}H_{18}BrNO_6$
Formula Weight 412



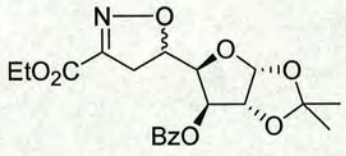
Using the general method above; triethylamine (346 mg, 3.42 mmol) in sodium-dried ether (40 ml) was added, over 72 hours, to the stirred mixture of 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**58**) (1.04 g, 3.59 mmol) and dibromoformaldoxime (**66**) (608 mg, 3.00 mmol) in sodium-dried ether (50 ml). The solution was then stirred for a further ten hours, and poured into water (100 ml). The aqueous layer was extracted with ether (3 x 50 ml), the combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The diastereomeric cycloadducts were separated from the unreacted alkene using dry flash chromatography (silica, 0→100% ether in hexane; gradient elution). The column afforded, in order of elution, unreacted alkene (600 mg, 58%) and a pair of inseparable diastereomeric cycloadducts as a solid (421 mg, 67% based on consumed **58**) in the ratio of 13:87 as determined by ^{1}H NMR spectroscopy from the signal for the anomeric proton (1-H); mp 116-118°C.

The major isomer was isolated by recrystallisation of the crude mixture from ethanol (131 mg, 30%); mp 130-137°C; $[\alpha]_D^{21}$ –76.7 (c = 0.41, $CHCl_3$); R_f 0.68 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.30, 1.52 (6H, 2 x s, $C(CH_3)_2$), 3.26 (1H, dd, 6b-H), 3.42 (1H, dd, 6a-H), 4.45 (1H, dd, 4-H), 4.64 (1H, d, 2-H), 4.96 (1H, ddd, 5-H), 5.50 (1H, d, 3-H), 5.96 (1H, d, 1-H), 7.39-8.02 (5H, m, Ph); *J*(x-y)/Hz 1-2 3.7, 2-3 ~0, 3-4 3.1, 4-5 6.9, 5-6a 7.4, 5-6b 10.6, 6a-6b, 17.5; δ_C (63 MHz, $CDCl_3$) 26.6, 27.2 ($C(CH_3)_2$), 44.5 (C-6), 76.7, 78.6, 79.4, 83.9 (C-2, C-3, C-4, C-5), 105.5 (C-1), 113.0 ($C(CH_3)_2$), 129.1, 130.1, 129.5 (5 x CHPh), 134.2 (qCPh), 138.1 (C-7), 165.4 (PhCO); *m/z*(FAB) Found: Br^{79} M^++1 412.03870. $C_{17}H_{19}NO_6Br$ requires M^++1 412.03957; Found Br^{81} M^++1 414.0377. $C_{17}H_{19}NO_6Br$ requires M^++1 414.0281; Calc. For $C_{17}H_{18}BrNO_6$: C, 59.26; H, 5.68; N, 3.46. Found: C, 59.22; H, 5.45; N, 2.86%; diagnostic signals for minor isomer δ_H (250 MHz, $CDCl_3$) 4.69 (1H, d, 2-H), 6.27 (1H, d, 2-H); *J*(x-y)/Hz 1-2 3.8; unidentified peak at 5.95, possible due to an unisolated isomer.

3.4.3 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (82)

Lab. Book Ref. KG 12
Molecular Formula $C_{20}H_{23}NO_8$
Formula Weight 405



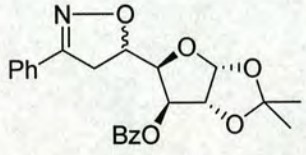
Using the general method above; triethylamine (482 mg, 4.77 mmol) in sodium-dried ether (40 ml) was added, over 72 hours, to the stirred mixture of 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**58**) (1.20 g, 4.15 mmol) (50 ml) and dibromoformaldoxime (**67**) (600 mg, 3.96 mmol) in sodium-dried ether. The solution was then stirred for a further ten hours, and poured into water (100 ml). The aqueous layer was extracted with ether (3 x 50 ml), the combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The diastereomeric cycloadducts were separated from the unreacted alkene using dry flash chromatography (silica, 0→100% ether in hexane; gradient elution). The column afforded, in order of elution, unreacted alkene (489 mg, 41%) and a pair of diastereomeric cycloadducts as a white solid (670 mg, 67%, based on consumed alkene) in a ratio of 13:87 (determined from ^{1}H NMR spectroscopy from the signal for the anomeric proton [1-H]); mp 90°C.

The major isomer was isolated by the recrystallisation of the crude mixture from ethanol; mp 108-110°C; R_f 0.70 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.31 (3H, t, CH_3CH_2), 1.32, 1.55 (6H, 2 x s, $C(CH_3)_2$), 3.23 (1H, dd, 6b-H), 3.43 (1H, dd, 6a-H), 4.29 (2H, q, CH_3CH_2), 4.45 (1H, dd, 4-H), 4.64 (1H, d, 2-H), 5.07 (1H, ddd, 5-H), 5.50 (1H, d, 3-H), 5.96 (1H, d, 1-H), 7.39-8.01 (5H, m, Ph); *J*(x-y)/Hz CH_3CH_2 7.1, 1-2 3.7, 2-3 nd, 3-4 3.1, 4-5 6.5. 5-6a 7.5, 5-6b 11.3, 6a-6b 17.9; δ_C (63 MHz, $CDCl_3$) 13.8 (CH_3CH_2), 25.9, 26.5 ($C(CH_3)_2$), 36.0 (C-6), 76.2, 78.7, 79.7, 83.2 (C-2, C-3, C-4, C-5), 104.8 (C-1), 112.4 ($C(CH_3)_2$), 128.4, 129.5, 133.53 (5 x CHPh), 128.8 (qCPh), 151.7 (EtCO), 160.2 (C-7), 164.8 (PhCO); *m/z*(FAB) Found: M^++1 406.1498. $C_{20}H_{24}NO_8$ requires M^++1 406.1502; diagnostic signals for minor isomer δ_H (250 MHz, $CDCl_3$) 4.68 (1H, d, 2-H), 6.02 (1H, d, 2-H); *J*(x-y)/Hz 1-2 3.8; unidentified peak at 5.95, possible due to an unisolated isomer.

3.4.4 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-phenyl-2-isoxazoline (83)

Lab. Book Ref. KG 14
Molecular Formula $C_{23}H_{23}NO_6$
Formula Weight 409



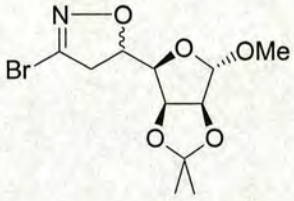
Using the general method above; triethylamine (238 mg, 2.35 mmol) in sodium-dried ether (40 ml) was added, over 48 hours, to the stirred mixture of 3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**58**) (611 mg, 2.11 mmol) (50 ml) and dibromoformaldoxime (**68**) (300 mg, 1.93 mmol) in sodium-dried ether. The solution was then stirred for a further ten hours, and poured into water (100 ml). The aqueous layer was extracted with ether (3 x 50 ml), the combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The diastereomeric cycloadducts were separated from the unreacted alkene using dry flash chromatography (silica, 0→100% ether in hexane; gradient elution). The column yielded, in

order of elution, unreacted alkene (137 mg, 22%) and a pair of diastereomeric cycloadducts as a solid (458 mg, 69%, based on consumed alkene) in a ratio of 16:84 (determined from ^{1}H NMR spectroscopy from the signal for the anomeric proton [1-H]); mp 137-138°C.

The major isomer was isolated by repeated recrystallisation from ethanol; mp 133°C; R_f 0.61 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.31, 1.52 (6H, 2 x s, $C(CH_3)_2$), 3.53 (1H, dd, 6b-H), 3.62 (1H, dd, 6a-H), 4.43 (1H, dd, 4-H), 4.70 (1H, d, 2-H), 5.09 (1H, ddd, 5-H), 5.60 (1H, d, 3-H), 5.99 (1H, d, 1-H), 7.34-8.07 (5H, m, Ph); *J*(x-y)/Hz 1-2 3.7, 2-3 nd, 3-4 3.1, 4-5 8.1, 5-6a 7.2, 5-6b 11.3, 6a-6b 17.0; δ_C (63 MHz, $CDCl_3$) 26.0, 26.5 ($C(CH_3)_2$), 38.2 (C-6), 76.2, 76.9, 79.3, 83.4 (C-2, C-3, C-4, C-5), 104.8 (C-1), 112.3 ($C(CH_3)_2$), 126.7, 128.4, 130.1 (5 x CHPh, Bz), 128.9 (qCPh, Bz), 128.6, 129.2 (5 x CHPh, Ph), 133.4 (qCPh, Ph), 156.5 (C-7), 164.9 (PhCO); *m/z*(FAB) Found: M^++1 410.1601. $C_{23}H_{23}NO_6$ requires M^++1 410.1604; diagnostic signals for minor isomer δ_H (250 MHz, $CDCl_3$) 3.24 (1H, dd, 6a-H), 3.39 (1H, dd, 6b-H), 4.74 (1H, d, 2-H), 4.56 (1h, dd, 4-H), 6.09 (1H, d, 2-H); *J*(x-y)/Hz 1-2 3.9, 2-3 nd, 3-4 3.7, 4-5 6.6 5-6a 8.4, 5-6b 10.9, 6a-6b 16.8; unidentified peak at ~5.95, possible due to an unisolated isomer.

3.4.5 3-Bromo-5-(methyl-1,2-*O*-isopropylidene-α-D-*lyxo*-furanos-4-yl)-2-isoxazoline (84)



Lab. Book Ref. KG 45
Molecular Formula $C_{11}H_{16}BrNO_5$
Formula Weight 322

Using the general method above; triethylamine (360 mg, 3.56 mmol) in sodium-dried ether (40 ml) was added, over 72 hours, to the stirred mixture of methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (**61**) (963 mg, 4.81 mmol) and dibromoformaldoxime (**66**) (605 mg, 2.98 mmol) in sodium-dried ether (50 ml). The solution was then stirred for a further ten hours, and poured into water (100 ml). The aqueous layer was extracted with ether (3 x 50 ml), the combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The diastereomeric cycloadducts were separated from the unreacted alkene using dry flash chromatography (silica, 0→100% ether in hexane; gradient elution). The column gave, in order of elution, unreacted alkene (764 mg, 79%) and a pair of diastereomeric cycloadducts

(296 mg, 92%, based on consumed alkene) as an oil in a ratio of 21:79 (determined by ^{1}H NMR spectroscopy from the signal for the anomeric proton [1-H]); $[\alpha]_D^{21}$ +8.52 (c = 2.18, $CHCl_3$); R_f 0.66 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.27, 1.43 (6H, 2 x s, $C(CH_3)_2$), 3.23 (1H, dd, 6b-H), 3.30 (3H, s, OMe), 3.35 (1H, dd, 6a-H), 4.11-4.13 (1H, dd, 4-H), 4.54 (1H, d, 2-H), 4.73 (1H, dd, 3-H), 4.90 (1H, s, 1-H), 4.91-4.97 (1H, ddd, 5-H); *J*(x-y)/Hz 1-2 ~0, 2-3 5.9, 3-4 3.7, 4-5 nd, 5-6a 8.4, 5-6b 10.7, 6a-6b 17.5; δ_C (63 MHz, $CDCl_3$) 24.0, 25.5 ($C(CH_3)_2$), 43.3 (C-6) 54.7 (OMe), 78.8, 78.9, 79.2, 84.5 (C-2, C-3, C-4, C-5), 107.0 (C-1), 112.6 ($C(CH_3)_2$), 137.9 (C-7); *m/z*(FAB) Found: M^++1 322.0340. $C_{12}H_{17}BrNO_5$ requires M^++1 322.0290; Calc. For $C_{11}H_{16}BrNO_5$: C, 40.99; H, 4.97; N, 4.97. Found: C, 40.42; H, 4.02; N, 4.38%.

3.5 Reactions of Cycloadducts

3.5.1 Reduction of Ester Groups of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (82)[87,88]

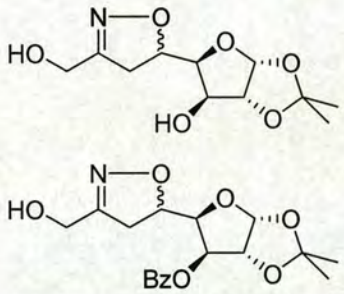
Lab. Book Ref. KG 365

90 Molecular Formula $C_{11}H_{17}NO_6$

Formula Weight 259

91 Molecular Formula $C_{18}H_{21}NO_7$

Formula Weight 363



Sodium borohydride (38 mg, 1.0 mmol) was added portionwise to a solution of the ester isoxazoline **82** (99 mg, 0.24 mmol) in ethanol (6 ml) and DCM (2 ml). The reaction mixture was stirred at room temperature until the disappearance of the starting material (3-4 h). The solution was poured into water (25 ml) and then extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*, this gave the two alcohols **90** and **91** as an inseparable white solid (14 mg).

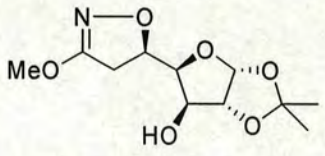
A twenty-fold excess of sodium borohydride (392 mg, 10.0 mmol) was added portionwise to a solution of the ester isoxazoline **82** (210 mg, 0. 519 mmol) in ethanol (35 ml). The reaction mixture was stirred at room temperature until the disappearance of the starting material (3-4 h). The solution was poured into water (25 ml) and then extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*, this gave the two alcohols **90** and **91** as a white solid (112 mg). The mass spectrum indicates

that the major product is alcohol **90** that has been deprotected in the 3-position; **90** δ_H (250 MHz, $CDCl_3$) 1.31, 1.53 (6H, 2 x s, $C(CH_3)_2$, 3.15-3.53 (2H, m, 6a-H, 6b-H), 4.13 (1H, d, 4-H), 4.37-4.43 (2H, m, 8a-H, 8b-H), 4.65 (1H, d, 2-H), 4.72-5.01 (1H, m, 5-H), 5.52 (1H, d, 3-H), 5.97 (1H, d, 1-H), 6.10 (1H, broad s, 8-OH), 7.00 (1H, broad s, 8-OH); *J*(x-y)/Hz 1-2 3.71, 2-3 nd, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd, 8a-8b nd; m/z (FAB) 260 and 364; diagnostic peaks for **91** δ_H (250 MHz, $CDCl_3$) 3.75-3.80 (2H, m, 6a-H, 6b-H), 4.07 (1H, d, 4-H), 7.41-8.03 (5 x CHPh).

3.5.2 Substitution Reactions[89]

3.5.2.1 5-(1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-methoxy-2-isoxazoline (92)

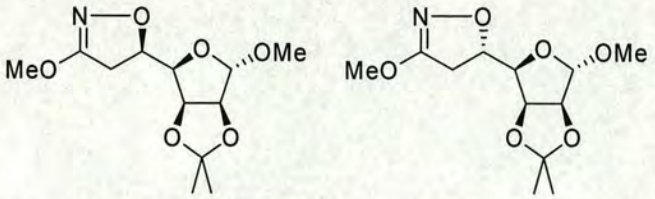
Lab. Book Ref. KG 56-1
Molecular Formula $C_{12}H_{17}NO_6$
Formula Weight 259



Isoxazoline **81** (*R*:*S* 87:13) (150 mg, 0.36 mmol) was dissolved in lithium methoxide/methanol solution (31 mg lithium dissolved in 15 ml dry methanol). The reaction mixture was heated at reflux until no starting material remained and was then allowed to stir for a further 30 min. The mixture was poured into ice-cold water (50 ml) and the product was extracted into ether (3 x 50 ml). The combined organics were dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the title compound as an oil containing only the *R*-isomer (63 mg, 66%, total; 72%, based on *R*-isomer content of starting material); $[\alpha]_D^{21}$ – 73.6 (c = 0.63, $CHCl_3$); R_f 0.42 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.34, 1.52 (6H, 2 x s, $C(CH_3)_2$), 3.05 (1H, d, OH), 3.09 (1H, dd, 6b-H), 3.18 (1H, dd, 6a-H), 3.88 (3H, s, CH_3), 4.23 (1H, dd, 4-H), 4.39 (1H, dd, 3-H), 4.57 (1H, d, 2-H), 4.91 (1H, ddd, 5-H), 5.96 (1H, d, 1-H); *J*(x-y)/Hz 1-2 3.6, 2-3 nd, 3-4 2.8, 3-OH 4.2, 4-5 11.1, 5-6a 9.8, 5-6b 7.7, 6a-6b 16.7; δ_C (63 MHz, $CDCl_3$) 26.6, 27.2 ($C(CH_3)_2$), 36.6 (C-6), 57.9 (OCH_3), 74.8, 78.5, 81.4, 85.8 (C-2, C-3, C-4, C-5), 105.6 (C-1), 112.3 ($C(CH_3)_2$), 168.8 (C-7); *m/z*(FAB) Found: M^++1 260.1134. $C_{11}H_{18}N_6O_6$ requires M^++1 260.1136.

3.5.2.2 3-Methoxy-5-(methyl-1,2-*O*-isopropylidene-α-D-*lyxo*-furanos-4-yl)-2-isoxazoline (93)

Lab. Book Ref. KG 59-1, 59-2
Molecular Formula $C_{12}H_{19}NO_6$
Formula Weight 273



Isoxazoline **84** (*R*:*S* 79:21) (152 mg, 0.47 mmol) was dissolved in lithium methoxide/methanol solution (23 mg lithium dissolved in 10 ml dry methanol). The reaction mixture was heated at reflux until no starting material remained and was then allowed to stir for a further 30 min. The mixture was poured into ice-cold water (50 ml) and the product was extracted into ether (3 x 50 ml). The combined organics were dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the title compound as an oil containing a mixture of the two isomers isomer (101 mg, 78%). The two isomers were partially separated using column chromatography (silica, 0→100% ether in hexane; gradient elution); **93a** (82 mg, 63%, total; 80%, based on *R*-isomer content in starting material); $[\alpha]_D^{21}$ +28.6 (c = 0.52, $CHCl_3$); R_f 0.54 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.32, 1.46 (6H, 2 x s, $C(CH_3)_2$), 3.04 (1H, dd, 6b-H), 3.15 (1H, dd, 6a-H), 3.35 (3H, s, C-1-O*C*H_3), 3.88 (3H, s, C-7-O*C*H_3), 4.13 (1H, dd, 4-H), 4.58 (1H, d, 2-H), 4.78 (1H, dd, 3-H), 4.90 (1H, s, 1-H), 4.94 (1H, ddd, 5-H); *J*(x-y)/Hz 1-2 ~0, 2-3 5.9, 3-4 3.7, 4-5 5.5, 5-6a 8.1, 5-6b 10.1. 6a-6b 16.7; δ_C (63 MHz, $CDCl_3$) 24.8, 26.2 ($C(CH_3)_2$), 35.2 (C-6), 55.2 (C-1-O*C*H_3), 57.7 (C-7-O*C*H_3), 79.2, 79.6, 79.7, 85.2 (C-2, C-3, C-4, C-5), 107.6 (C-1), 113.1 ($C(CH_3)_2$), 168.5 (C-7); **93b** (19 mg, 15%, total; 70%, *S*-isomer); $[\alpha]_D^{21}$ +65.3 (c = 0.92, $CHCl_3$); R_f 0.47 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.26, 1.41 (6H, 2 x s, $C(CH_3)_2$), 2.76 (1H, dd, 6b-H), 3.15 (1H, dd, 6a-H), 3.3 (3H, s, C-1-O*C*H_3), 3.84 (3H, s, C-7-O*C*H_3), 4.08 (1H, dd, 4-H), 4.54 (1H, d, 2-H), 4.68 (1H, dd, 3-H), 4.83 (1H, ddd, 5-H), 4.95 (1H, s, 1-H); *J*(x-y)/Hz 1-2 ~0, 2-3 5.9, 3-4 3.8, 4-5 8.5, 5-6a 10.0, 5-6b 8.7, 6a-6b 16.6; δ_C (63 MHz, $CDCl_3$) 24.6, 25.8 ($C(CH_3)_2$), 35.1 (C-6), 54.7 (C-1-O*C*H_3), 57.2 (C-7-O*C*H_3), 79.6, 80.4, 81.0, 84.7 (C-2, C-3, C-4, C-5), 107.4 (C-1), 112.8 ($C(CH_3)_2$), 167.5 (C-7); *m/z*(FAB) Found: M^++1 274.1291. $C_{12}H_{20}NO_6$ requires M^++1 457.1281.

3.5.3 Ring Opening Reactions

3.5.3.1 Attempted Ring Opening of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-carbethoxy-2-isoxazoline (82)[90]

Lab Book Ref. KG 101

Molybdenum hexacarbonyl (30 mg, 0.11 mmol) was added to a solution of isoxazoline **82** (101 mg, 0.25 mmol) in acetonitrile (15 ml) containing 5 drops of water. The resulting suspension was heated to reflux with stirring, after 1 h an additional portion of $Mo(CO)_6$ (15 mg, 0.06 mmol) was added and heating continued for 3 h. Column chromatography yielded the starting material quantitatively and no product was observed.

3.5.3.2 Attempted Ring Opening of 5-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-phenyl-2-isoxazoline (83)[17]

Lab Book Ref. KG 100

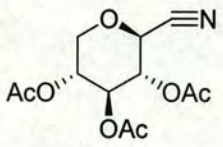
Isoxazoline **83** (100 mg, 0.25 mmol) and boric acid (15 mg, 6 eq.) were dissolved in methanol:water (6 ml, 5:1), to this six spatula tips of Raney nickel catalyst were added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 24 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting oil was co-evaporated with methanol to remove the residual boric acid, this yielded a white solid (6 mg, 6%) that was identified as the staring material and an unidentified brown oil (4 mg).

3.6 Synthesis of Exoglycals

3.6.1 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-acetal-1-deoxy-D-*xylo*-hex-1-enitol (62)[97]

3.6.1.1 2,6-Anhydro-3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitrile (107)[105]

Lab. Book Ref. KG 55
Molecular Formula $C_{12}H_{15}NO_7$
Formula Weight 285



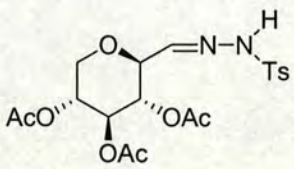
Acetylated nitromethyl xylose **70** (150 mg, 0.47 mmol) was dissolved in pyridine (3 ml) and cooled in an ice bath. To this PCl_3 (1.1 eq, 0.05 ml, 0.52 mmol) was added and the mixture was stirred overnight at room temperature. Ice-cold 1M HCl (20 ml) was added to the solution and was stirred for 20 min. The product was extracted into chloroform (3 x 10 ml); the combined organics were washed with sat. $NaHCO_3$ (2 x 10 ml) and water (10 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*, to give the title compound as a white solid (113 mg, 84%); mp 128-129°C (lit.[105] 131-132°C); $[\alpha]_D^{18}$ –36.7 (c = 0.90, $CHCl_3$); R_f 0.54 (Et_2O); δ_H (250 MHz, $CDCl_3$) 2.03, 2.06, 2.07 (9H, 3 x s, CH_3), 3.56 (1H, dd, 6b-H), 4.18 (1H, dd, 6a-H), 4.46 (1H, d, 2-H), 4.83-4.90 (1H, m, 5-H), 5.04-5.07 (2H, m, 3-H, 4-H); *J*(x-y)/Hz 2-3 6.9, 3-4 nd, 4-5 nd, 5-6a 4.0, 5-6b 6.8, 6a-6b 12.4; δ_C (63 MHz, $CDCl_3$) 20.3, 20.5 ($COCH_3$), 65.1 (C-6), 65.3, 66.8, 67.6, 68.7 (C-2, C-3, C-4, C-5), 114.3 (C-1), 168.8, 169.2, 169.4 (3 x $COCH_3$). *m/z*(FAB) Found: M^++1 286.0921. $C_{12}H_{16}NO_7$ requires M^++1 286.0927.

3.6.1.2 2,6-Anydro-3,4,5-tri-*O*-acetyl-β-D-xylose tosylhydrazone (108)[97,108]

Lab. Book Ref. KG 67

Molecular Formula $C_{19}H_{24}N_2O_9S$

Formula Weight 456

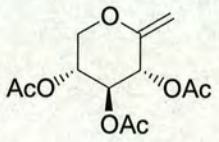


Raney nickel (1.5 g, from an aqueous suspension, Sigma) was added, at room temperature, to a vigorously stirred solution of pyridine (5.7 ml), acetic acid (3.4 ml) and water (3.4 ml). Then sodium hypophosphate (740 mg, 8.40 mmol), tosylhydrazine (320 mg, 1.70 mmol) and the acetylated xylose nitrile **107** (303 mg, 1.06 mmol) were added to the mixture that was left to stir overnight. The insoluble materials were filtered through a celite pad, which was washed with DCM (10 ml). The organic layer of the filtrate was separated, washed sequentially with water (3 ml), 10% HCl (2 x 3 ml), cold saturated sodium hydrogen carbonate (2 x 3 ml), water (3 ml) and then dried ($MgSO_4$). The solution was concentrated and the traces of pyridine were removed by repeated co-evaporations with toluene. The residue was purified by column chromatography (silica, 0→100% ether in hexane; gradient elution), to give the title compound as a white solid (416 mg, 86%); R_f 0.33 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.71, 2.00, 2.38 (9H, 3 x s, $COCH_3$), 2.00 (CH_3), 3.27 (1H, t, 6b-H), 3.86 (1H, dd, 2-H), 4.07 (1H, dd, 6a-H), 4.87 (1H, t, 3-H), 4.87-4.99 (1H, m, 5-H), 5.21 (1H, t, 4-H), 6.94 (1H, d, 1-H), 7.27-7.79 (4H, m, Ph), 8.90 (1H, s, NH); *J*(x-y)/Hz 1-2 6.4, 2-3 9.7, 3-4 9.6, 4-5 9.5, 5-6a 5.6, 5-6b 10.9, 6a-6b 11.1 δ_C (63 MHz, $CDCl_3$) 20.4, 20.5, 21.4 (3 x

$COCH_3$), 20.5 (CH_3), 65.7 (C-6), 68.8, 69.5, 72.4 (C-3, C-4, C-5), 78.0 (C-2), 127.8, 129.5, 135.1 (5 x CHPh), 144.0 (C-1), 144.1 (qCPh), 169.8, 170.0, 170.5 (3 x $COCH_3$); *m/z*(FAB) Found: M^++1 457.1286. $C_{19}H_{25}N_2O_9S$ requires M^++1 457.1281.

3.6.1.3 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-D-*xylo*-hex-1-enitol (62)[97,108]

Lab. Book Ref. KG 116
Molecular Formula $C_{12}H_{16}O_7$
Formula Weight 272

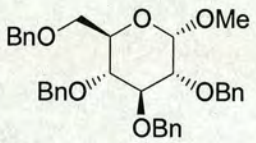


Sodium hydride (76 mg, 3.2 mmol) was added to dry 1,4-dioxane (10 ml). The stirred suspension was heated at reflux and had 2,6-anhydro-3,4,5-*O*-acetyl-β-D-xylose tosylhydrazone (**108**) (125 mg, 0.27 mmol) in dry 1,4-dioxane (25 ml) added in a dropwise fashion. When the reaction was complete (tlc) the mixture was cooled and the insoluble materials were filtered off. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica, 0→100% ether in hexane; gradient elution) to give the title compound as a white solid (161 mg, 51%); R_f 0.64 (Et_2O); δ_H (250 MHz, $CDCl_3$) 2.29, 2.34 (9H, 3 x s, $COCH_3$), 3.80 (1H, dd, 6b-H), 4.42 (1H, dd, 6a-H), 4.71 (1H, dd, 1a-H), 4.97 (1H, dd, 1b-H), 5.30 (1H, ddd, 5-H), 5.35 (1H, t, 4-H), 5.62 (1H, d, 3-H); *J*(x-y)/Hz 1a-1b 1.5, 1a-3 0.8, 1b-3 0.5, 3-4 7.7, 4-5 7.6, 5-6a 4.7, 5-6b 8.2. 6a-6b 11.2; δ_C (63 MHz, $CDCl_3$) 21.2 (3 x $COCH_3$), 67.4 (C-6), 69.2, 72.6 (C-3, C-4, C-5), 99.4 (C-1), 154.0 (C-2), 169.7, 170.2 (3 x $COCH_3$); *m/z*(FAB) Found: M^++1 273.0970. $C_{12}H_{17}O_7$ requires M^++1 273.0974.

3.6.2 Synthesis of 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (59)

3.6.2.1 Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (112)[158]

Lab. Book Ref. KG 169
Molecular Formula $C_{35}H_{38}O_6$
Formula Weight 554

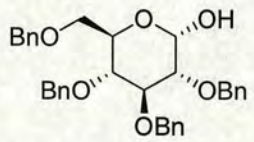


To a cooled suspension (5°C) of NaH (60% w/w, 12.36 g, 0.3 mol) in anhydrous DMF (80 ml) was added a solution of methyl α-D-glucopyranoside (10 g, 0.05 mol) in DMF (100ml) from a dropping funnel over 30 min. and the mixture stirred for 1 h while warming to room

temperature. After recooling to 5°C, benzyl bromide (37 ml, 0.31 mmol) was added in three portions *via* a syringe and the reaction stirred for 20 h. After cautiously quenching the excess NaH with methanol (60 ml) the reaction mixture was partitioned between toluene (200 ml) and water (200 ml) and the aqueous phase was further extracted with toluene (2 x 100 ml). The organic parts were washed with water (150 ml), brine (150 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Addition of triethylamine (20 ml) to the crude oil followed by stirring for one hour at room temperature converted excess benzyl bromide into benzyl triethylammonium bromide, which was removed by addition of ether (200 ml) and water (150 ml). The organic phase was washed with brine (150 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave a pale yellow oil, which was taken through to the next stage without further purification. However, if purification was required then this would be achieved by column chromatography (silica, 19:1→1:1 ethyl acetate in petroleum ether, gradient elution) to give the title compound as a colourless oil (27.14 g, 87%); $[\alpha]_D^{18}$ +19.7 (c = 1.0, $CHCl_3$) [lit.[109] +18.7 (c = 1.5, $CHCl_3$)]; R_f 0.69 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.39 (3H, s, OMe), 3.60 (1H, d, 2-H), 3.62-3.74 (4H, m, 4-H, 5-H, 6a-H, 6b-H), 4.00 (1H, t, 3-H), 4.64 (1H, d, 1-H), 4.46-5.28 (8H, m, CH_2Ph), 7.30-7.39 (20H, m, Ph); *J*(x-y)/Hz 1-2 3.6, 2-3 9.1, 3-4 9.1, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 55.0 (OMe) 68.3 (C-6), 69.3, 77.5, 79.7, 82.0 (C-2, C-3, C-4, C-5), 73.2, 73.3, 75.0, 75.6 (4 x CH_2Ph), 98.1 (C-1), 127.4-128.3 (20 x CHPh), 137.8, 138.0, 138.1, 138.6 (4 x qCPh).

3.6.2.2 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (113)[159]

Lab. Book Ref. KG 174
Molecular Formula $C_{34}H_{36}O_6$
Formula Weight 540

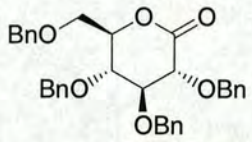


To a solution of the glycoside **112** (8.07 g, 14.6 mmol) in glacial acetic acid (100ml) was added 2M aq. sulphuric acid (50 ml, 100 mmol) and the mixture stirred at 90°C for 18 h. After cooling to room temperature, the acetic acid was removed *in vacuo* and DCM (100 ml) added and the organic layer was washed with saturated aq. sodium bicarbonate (50 ml) and brine (50 ml). The solvent was removed under reduced pressure to give the crude product as a white solid that was recrystallised from methanol to afford the title compound as fine colourless needles (2.79 g, 35%); mp 150°C (lit.[110] 151-152°C); $[\alpha]_D^{18}$ +20.8 (c = 0.96, $CHCl_3$) [lit.[110] +22 (c = 1, $CHCl_3$)]; R_f 0.51 (petroleum ether:ethyl acetate, 1:1); δ_H (250

MHz, $CDCl_3$) 3.86-4.00 (5H, m, 2-H, 4-H, 5-H, 6a-H, 6b-H), 4.31 (1H, t, 3-H), 5.02-5.29 (8H, m, CH_2Ph), 5.53 (1H, d, 1-H), 7.54-7.64 (20H, m, Ph); *J*(x-y)/Hz 1-2 3.5, 2-3 9.3, 3-4 9.3, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 67.9 (β C-6), 69.5, 77.1, 79.3, 81.1 (α C-2, α C-3, α C-4, α C-5), 72.5, 72.8, 74.3, 75.1 (4 x α & β CH_2Ph), 73.9, 77.1, 82.4, 83.9 (β C-2, β C-3, β C-4, β C-5), 90.6 (α C-1), 96.8 (β C-1), 127.0-127.8 (20 x CHPh), 137.1-138.0 (4 x qCPh).

3.6.2.3 2,3,4,6-Tetra-*O*-benzyl-D-*glucono*-1,5-lactone (114)[36]

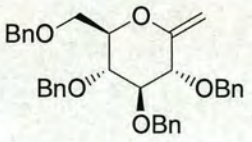
Lab. Book Ref. KG 176
Molecular Formula $C_{34}H_{34}O_6$
Formula Weight 538



A solution of the lactol **113** (3.00 g, 5.6 mmol) in a mixture of acetic anhydride (10 ml) and dimethyl sulphoxide (15 ml) was stirred at room temperature for 24 h, quenched with water (70 ml), stirred for a further 15 min. and extracted with DCM (3 x 30 ml). The organic phase was washed with saturated aq. $NaHCO_3$ (30 ml), dried ($MgSO_4$) and purified by column chromatography (elution with light petroleum:ethyl acetate, 1:1) to give the title compound as a yellow oil (2.27 g, 76%); $[\alpha]_D^{18}$ +40.2 (c = 0.82, $CHCl_3$) [lit.[111] +79 (c = 1, $CHCl_3$)]; R_f 0.67 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.78-3.91 (2H, m, 6a-H, 6b-H), 4.05-4.15 (2H, m, 3-H, 4H), 4.24-4.32 (1H, m, 2-H), 4.59-4.92 (8H, m, 5-H & CH_2Ph), 5.16 (1H, d, CH_2Ph), 7.37-7.59 (20H, m, Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 68.1 (C-6), 73.4, 73.6, 73.8 (4 x CH_2Ph), 75.9, 77.2, 78.0, 80.8 (C-2, C-3, C-4, C-5), 127.7, 127.8, 127.9, 128.3 (20 x CHPh), 136.8, 137.4, 137.4 (4 x qCPh), 169.2 (C-1); *m/z*(FAB) Found: M^++1 539.2425. $C_{34}H_{35}O_6$ requires M^++1 539.2434.

3.6.2.4 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (59)[95d]

Lab. Book Ref. KG 195
Molecular Formula $C_{35}H_{36}O_5$
Formula Weight 536



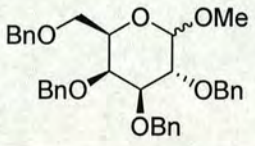
A solution containing the lactone **114** (2.0 g, 3.8 mmol) and dimethyl titanocene (**115**) (2 eq, 1.52 g, 7.3 mmol) in toluene (50 ml) was stirred at 70°C in the dark for 24 h. After cooling, the solvent was removed *in vacuo* and the residue was chromatographed (silica, 9:1→4:1,

ethyl acetate in hexane with 1% NEt_3) to give a yellow solid. Recrystallisation from hexane gave the title compound as fine, white needles (1.22 g, 61%); mp 65°C (lit.[95d] 65-68°C); $[\alpha]_D^{18}$ +48.7 (c = 0.78, $CHCl_3$) [lit.[95d] +58.4 (c = 1.5, DCM)]; R_f 0.20 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 3.94-4.08 (5H, m, 4-H, 5-H, 6-H, 7a-H, 7b-H), 4.26 (1H, broad, 3-H), 4.80-5.20 (10H, m, CH_2Ph, 1a-H, 1-H), 7.56-7.67 (20H, m, Ph); *J*(x-y)/Hz 3-4 7.1, 4-5 nd, 5-6, nd, 6-7a nd, 6-7b nd, 7a-7b nd; δ_C (63 MHz, $CDCl_3$) 68.0 (C-7), 72.1, 72.8, 73.8, 73.82 (4 x CH_2Ph), 76.9, 77.9, 78.3, 84.0 (C-3, C-4, C-5, C-6), 94.1 (C-1), 127.0, 127.1, 127.2, 127.7, 127.8 (20 x CHPh), 137.2, 137.3, 137.4, 137.7 (4 x qCPh), 155.7 (C-2); *m/z*(FAB) Found: M^++1 537.2631. $C_{35}H_{37}O_5$ requires M^++1 537.2641.

3.6.3 Synthesis of 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-1-enitol (65)

3.6.3.1 Methyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (117)[112,160]

Lab. Book Ref. KG 246
Molecular Formula $C_{35}H_{38}O_6$
Formula Weight 554

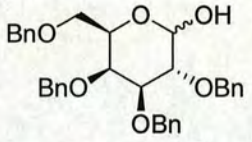


D-Galactose (6.00 g, 33.3 mmol) was dissolved in a 1% solution of hydrogen chloride in dry methanol [formed by the careful addition of acetyl chloride (0.68 ml) to dry methanol (40 ml)]. The solution was heated, under nitrogen, at reflux for 7 h then cooled rapidly in a water-bath and stored at 0 °C overnight. The crystals produced were then filtered, washed rapidly with cold methanol (3 x 50 ml) and dried *in vacuo*. The combined filtrate and washings were refluxed for 3.5 h, and the methanol was removed *in vacuo* till ~13 ml remained and the residue was treated as above to afford a second crop of crystals that were taken on to the next stage.

The solid produced above was dissolved in DMF (100 ml), this was added to sodium hydride (12.39 g, 309 mmol) in DMF (80 ml). The mixture was cooled and benzyl bromide (37 ml, 312 mmol) was added. Work up was identical to that for the glucose analogue **112** and resulted in the title compound as a brown oil (14.37 g, 78% over two steps); $[\alpha]_D^{18}$ +11.2 (c = 0.98, $CHCl_3$); R_f 0.67 (petroleum ether:ethyl acetate, 1:1); δ_H(250 MHz, $CDCl_3$) 3.40 (3H, s, OMe), 3.60-3.76 (5H, m, 2-H, 4-H, 5-H, 6a-H, 6b-H), 4.12 (1H, t, 3-H), 4.46-4.87 (9H, m, 1-H, CH_2Ph), 7.27-7.36 (20H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3 9.2, 3-4 9.2, 4-5 nd, 5-6a nd, 5-6b

nd, 6a-6b nd; δ_C(63 MHz, $CDCl_3$) 54.47 (α OMe), 56.41 (β OMe), 59.69 (α 6C), 67.76 (β 6C), 69.34, 74.13, 76.94, 77.15, 79.12, 81.43, 81.61, 93.94, (α & β CH, 2C, 3C, 4C, 5C), 68.19, 72.78, 74.06, 74.14, 74.33, 75.07 (4 x α & β CH_2Ph), 97.51 (α 1C), 104.01 (β 1C), 126.90-127.75 (20 x CHPh), 137.21-138.10 (4 x qCPh).

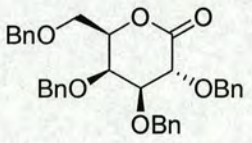
3.6.3.2 2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose (118)[160a]



Lab. Book Ref. KG 255
Molecular Formula $C_{34}H_{36}O_6$
Formula Weight 540

Employing an identical method to that used for the glucose analogue **113**, the title compound was produced by dissolving methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (**117**) (7.98 g, 14.4 mmol) in glacial acetic acid (100 ml) and 2M sulphuric acid (50 ml). The reaction mixture was then heated overnight at 90°C to yield on work up the desired product as a white solid (3.39 g, 44%); mp 147-148°C; $[\alpha]_D^{18}$ +17.3 (c = 1.04, $CHCl_3$) [lit.[160b] +13.1 (c = 1.6 $CHCl_3$)]; R_f 0.53 (major) 0.68 (minor) (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.35-3.64 (5H, m, 2-H, 3-H, 5-H, 6a-H, 6b-H), 4.00 (1H, t, 4-H), 4.41-4.96 (9H, m, CH_2Ph, 1-H), 7.23-7.32 (20H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3 nd, 3-4 9.1, 4-5 9.1, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 67.9 (α C-6), 68.2 (β C-6), 72.4, 72.7, 74.0, 74.3, 75.0 (4 x α & β CH_2Ph), 69.4, 73.8, 77.1, 79.3, 81.0, 82.4, 83.9 (α & β C-2, C-3, C-4, C-5), 90.5 (α C-1), 96.8 (βC-1), 126.9-127.8 (20 x CHPh), 137.0-138.0 (4 x qCPh).

3.6.3.3 2,3,4,6-Tetra-*O*-benzyl-D-*galacto*-1,5-lactone (119)[36]



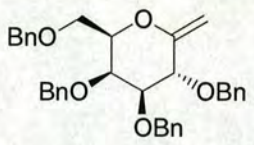
Lab. Book Ref. KG 258
Molecular Formula $C_{34}H_{34}O_6$
Formula Weight 538

The title compound was produced using the same oxidation method to that employed for the glucose analogue **114**; 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose (**118**) (3.00 g, 5.6 mmol) was dissolved in a mixture of acetic anhydride (10 ml) and DMSO (15 ml) this was stirred overnight to afford the product as a yellow oil on work up (2.90 g, 97%); $[\alpha]_D^{18}$ +47.0 (c = 1.68, $CHCl_3$) [lit.[160c] +75.2 ($CHCl_3$)]; R_f 0.72 (petroleum ether:ethyl acetate, 1:1); δ_H (250

MHz, $CDCl_3$) 3.82-3.85, 4.05-4.11 (5H, 2 x m, 3-H, 4-H, 5-H, 6a-H, 6b-H), 4.27 (1H, d, $J_{2,3}$ 6.7, 2-H), 4.57-4.76 (8H, m, CH_2Ph), 7.34-7.52 (20H, m, Ph); *J*(x-y)/Hz 2-3 6.7, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 67.9 (6C), 72.6, 73.0, 73.4, 73.6 (4 x CH_2Ph), 75.5, 76.7, 78.0, 80.7 (C-2, C-3, C-4, C-5), 127.7-128.3 (20 x CHPh), 136.7-138.4 (4 x qCPh), 169.2 (1C). ν_{max} (film) 3088, 3063, 3032, 2981, 2913, 2870, 1755 and 1241 cm^{-1}.

3.6.3.4 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-1-enitol (65)[161]

Lab. Book Ref. KG 264
Molecular formula $C_{35}H_{36}O_5$
Formula Weight 536

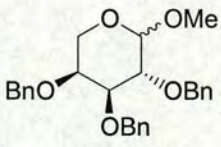


The title compound was produced using the same olefination method as that employed for the glucose analogue **59**; 2,3,4,6-tetra-*O*-benzyl-D-*galacto*-1,5-lactone (**119**) (2.02 g, 3.8 mmol,) was refluxed in toluene (50 ml) with dimethyl titanocene (**115**) (1.6 g, 7.7 mmol) to give the title compound as a brown oil (802 mg, 40%); $[\alpha]_D^{18}$ +50.0 (c = 0.44, $CHCl_3$); R_f 0.39 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 3.96-4.02 (5H, m, 4-H, 5-H, 6-H, 7a-H, 7b-H), 4.21 (1H, d, $J_{3,4}$ 7.1, 3-H), 4.74-5.15 (10H, m, CH_2Ph, 1a-H, 1b-H), 7.51-7.61 (20H, m, Ph); *J*(x-y)/Hz 3-4 7.1, 4-5 nd, 5-6 nd, 6-7a nd, 6-7b nd, 7a-7b nd; δ_C (63 MHz, $CDCl_3$) 68.0 (C-7), 72.1, 72.9, 73.8 x 2 (4 x CH_2Ph), 76.8, 77.9, 78.2, 84.0 (C-3, C-4, C-5, C-6), 94.1 (C-1), 127.0-127.8 (20 x CHPh), 137.2, 137.3, 137.6, 137.6 (4 x qCPh), 155.6 (C-2); *m/z*(FAB) Found: M^++1 537.2654. $C_{35}H_{37}O_5$ requires M^++1 537.2641.

3.6.4 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-L-*arabino*-hex-1-enitol (64)

3.6.4.1 Methyl 2,3,4-tri-*O*-benzyl-L-arabinopyranoside (121)[112,162]

Lab. Book Ref. KG 243
Molecular Formula $C_{27}H_{30}O_5$
Formula Weight 434



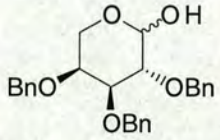
L-arabinose (5.00 g, 33.3 mmol) was dissolved in a 1% solution of hydrogen chloride in dry methanol [formed by the careful addition of acetyl chloride (0.68 ml) to dry methanol (40

ml)]. The solution was heated at reflux for 7 h under nitrogen, then cooled rapidly in a water-bath and stored at 0°C overnight. The crystals produced were then filtered, washed rapidly with cold methanol (3 x 50 ml) and dried *in vacuo*. The combined filtrate and washings were boiled under reflux for 3.5 h, and the methanol was removed *in vacuo* till ~13 ml remained and the residue was treated as above to give a second crop of crystals that were taken on to the next stage without further purification.

The title compound was prepared using the same benzylation method as that employed for the glucose analogue **112**; methyl L-arabinopyranoside (**120**) (7.71 g, 47 mmol) was dissolved in 100 ml DMF, to which was added sodium hydride (12.16 g, 0.30 mol) in DMF (80 ml). This mixture was cooled and benzyl bromide (37 ml, 312 mmol) was added, work up afforded the title compound as a brown oil (19.92 g, 68% over two steps); $[\alpha]_D^{18}$ +41.5 (c = 2.00, $CHCl_3$); R_f 0.57 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.60 (3H, s, OMe), 3.83-3.97 (3H, m, 2-H, 3-H, 4-H), 4.10 (1H, dd, 5a-H), 4.24 (1H, dd, 5Hb), 4.84-5.03 (9H, m, 1-H, CH_2Ph), 7.52-7.58 (15H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3 nd, 3-4 nd, 4-5a 3.4, 4-5b 2.1, 5a-5b 10.2; δ_C (63 MHz, $CDCl_3$) 55.3 (OMe), 60.0 (C-5), 71.6, 72.6, 73.5 (3 x CH_2Ph), 73.9, 76.2, 77.1 (C-2, C-3, C-4), 99.2 (C-1), 127.3-128.2 (15 x CHPh), 138.2, 138.5, 138.6 (3 x qCPh).

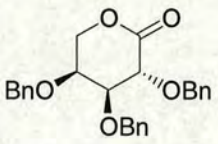
3.6.4.2 2,3,4-Tri-*O*-benzyl-L-arabinopyranose (122)[163]

Lab. Book Ref. KG 248
Molecular Formula $C_{26}H_{28}O_5$
Formula Weight 420



Duplicating the method used for the glucose analogue **113**, the title compound was produced by dissolving methyl 2,3,4-tri-*O*-benzyl-L-arabinopyranoside (**121**) (6.27 g, 14.4 mmol) in glacial acetic acid (100 ml) and 2M sulphuric acid (50 ml). The reaction mixture was then heated overnight at 90°C to yield, on work up, the desired product as a white solid (6.07 g, 52%) mp 65°C (lit.[95d] 69-70°C); $[\alpha]_D^{18}$ +34.6 (c = 0.78, $CHCl_3$) [lit.[163] +36.6 (c = 1.83 $CHCl_3$)]; R_f 0.51 (petroleum ether:EtOAc, 1:1); δ_H (250 MHz, $CDCl_3$) 3.93-4.30 (5H, m, 2-H, 3-H, 4-H, 5a-H, 5b-H), 4.82-5.10 (7H, m, 1-H, CH_2Ph), 7.58-7.66 (15H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3, nd, 3-4 nd, 4-5a nd, 4-5b nd, 5a-5b nd; δ_C (63 MHz, $CDCl_3$) 58.4 (α C-5), 60.7 (β C-5), 71.4, 72.5, 73.4 (3 x α & β CH_2Ph), 71.9, 75.4, 77.4 (α & β C-2, C-3, C-4), 91.9 (α C-1), 93.8 (β C-1), 127.5-128.3 (15 x CHPh), 137.3-138.2 (3 x qCPh).

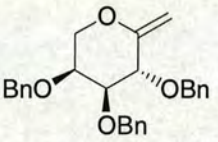
3.6.4.3 2,3,4-Tri-*O*-benzyl-L-*arabino*-1,5-lactone (123)[164]



Lab. Book Ref. KG 253
Molecular Formula $C_{26}H_{26}O_5$
Formula Weight 418

The title compound was produced using the same oxidation method as that employed for the glucose analogue **114**; 2,3,4-tri-*O*-benzyl-L-arabinopyranose (**122**) (2.34 g, 5.6 mmol) was dissolved in a mixture of acetic anhydride (10 ml) and DMSO (15 ml) this was stirred overnight. Work up gave the product as a yellow oil (2.24 g, 96%); $[\alpha]_D^{18}$ +38.7 (c = 1.06, $CHCl_3$); R_f 0.68 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 4.14-4.44 (5H, m, 2-H, 3-H, 4-H, 5a-H, 5b-H), 4.89-5.07 (6H, m, CH_2Ph), 7.61-7.69 (15H, m, Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5a nd, 4-5b nd, 5a-5b nd; δ_C (63 MHz, $CDCl_3$) 59.8 (C-5), 70.9, 76.2, 76.9 (C-2, C-3, C-4), 71.3, 72.0, 74.3 (3 x CH_2Ph), 127.0-127.9 (15 x CHPh), 136.6, 137.0, 137.7 (3 x qCPh), 170.6 (C-1); ν_{max} (film) 3088, 3063, 3031, 3007, 2981, 2873, 1741 and 1242 cm^{-1}.

3.6.4.4 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-L-*arabino*-hex-1-enitol (64)



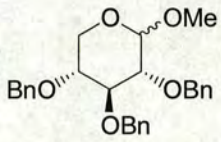
Lab. Book Ref. KG 267
Molecular Formula $C_{27}H_{28}O_4$
Formula Weight 416

The title compound was produced using the same olefination method as was employed for the glucose analogue **59**; 2,3,4-tri-*O*-benzyl-L-*arabino*-1,5-lactone (**123**) (1.62 g, 3.9 mmol) was refluxed in toluene (50 ml) with dimethyl titanocene (**115**) (1.6 g, 7.7 mmol) to yield the title compound as a brown oil (0.58 g, 35%); $[\alpha]_D^{18}$ +2.9 (c = 0.68, $CHCl_3$); R_f 0.41 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 3.99-4.07, 4.25-4.27 (4H, 2 x m, 4-H, 5-H, 6a-H, 6b-H), 4.33 (1H, d, 3-H), 4.70-5.00 (8H, m, CH_2Ph, 1a-H, 1b-H), 7.48-7.59 (15H, m, Ph); *J*(x-y)/Hz 3-4 6.0, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 66.7 (C-6), 71.2, 71.4, 72.3 (3 x CH_2Ph), 72.4, 76.1, 76.7 (C-3, C-4, C-5), 97.8 (C-1), 127.5-128.2 (15 x CHPh), 137.9, 138.0, 138.3 (3 x qCPh), 155.6 (C-2); *m/z*(FAB) Found: M^++1 417.2072. $C_{27}H_{29}O_4$ requires M^++1 417.2066.

3.6.5 Synthesis of 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*xylo*-hex-1-enitol (63)

3.6.5.1 Methyl 2,3,4-tri-*O*-benzyl-D-xylopyranoside (125)[112,165]

Lab. Book Ref. KG 244
Molecular Formula $C_{27}H_{30}O_5$
Formula Weight 434

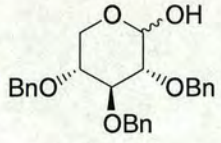


D-xylose (10.01 g, 66.6 mmol) was dissolved in a 1% solution of hydrogen chloride in dry methanol [formed by the careful addition of acetyl chloride (0.68 ml) to dry methanol (40 ml)]. The solution was heated at reflux for 7 h under nitrogen, then cooled rapidly in a water-bath and stored at 0°C overnight. The reaction mixture was neutralised using silver nitrate and filtered through a celite pad. The filtrate was evaporated to dryness to give a crude mixture of the methylated sugar as a sticky oil that was taken on to the next stage without further purification.

The title compound was prepared using the same method for the benzylation of a monomethylated sugar employed for the glucose analogue **112**; methyl D-xylopyranoside (**124**) (9.036 g, 55 mmol) was dissolved in 100 ml DMF, to which was added sodium hydride (12.20 g, 305 mmol) in DMF (80 ml). This mixture was cooled and benzyl bromide (37 ml, 312 mmol) was added, work up resulted in the title compound as a brown oil (15.01 g, 52% over two steps); $[\alpha]_D^{18}$ +12.5 (c = 3.36, $CHCl_3$) [lit.[162] +8 (c = 1 $CHCl_3$)]; R_f 0.71 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.56 (3H, s, OMe), 3.84-3.93 (3H, m, 2-H, 3-H, 4-H), 4.13-4.20 (2H, m, 5a-H, 5b-H), 4.60-4.79 (7H, m, 1-H, CH_2Ph), 7.31-7.50 (15H, m Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5a nd, 4-5b nd, 5a-5b nd; δ_C (63 MHz, $CDCl_3$) 55.1 (α OMe), 55.5 (β OMe), 69.2 (α C-5), 69.6 (β C-5), 71.8, 72.0, 72.4, 73.3, (α & β CH_2Ph), 75.7, 79.93, 81.3, 83.7, 86.7 (α & β C-2, C-3, C-4), 100.3 (α C-1), 108.0 (β C-1), 127.4-128.2 (15 x PhCH), 137.4-138.1 (3 x PhC).

3.6.5.2 2,3,4-Tri-*O*-benzyl-D-xylopyranose (126)[166]

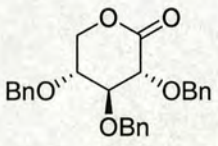
Lab. Book Ref. KG 249
Molecular Formula $C_{26}H_{28}O_5$
Formula Weight 420



Employing an identical method to that used for the glucose analogue **113**, the title compound was produced by dissolving methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranoside (**125**) (6.27 g, 14.4 mmol) in glacial acetic acid (100 ml) and 2M sulphuric acid (50 ml). The reaction mixture was then heated overnight at 90°C to give the desired product, on work up, as a white solid (3.58 g, 59%); mp 143-145°C; $[\alpha]_D^{18}$ +19.2 (c = 0.94, $CHCl_3$) [lit.[163a] +18.5 (c = 1 $CHCl_3$)]; R_f 0.63 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.42-3.54 (5H, m, 2-H, 4-H, 5a-H, 5b-H), 3.9 (1H, t, 3-H), 4.34-4.85 (7H, m, 1-H, CH_2Ph), 7.13-7.21 (15H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3 9.2, 3-4 9.2, 4-5a nd, 4-5b nd, 5a-5b nd; δ_C (63 MHz, $CDCl_3$) 67.9 (α C-5), 68.2 (β C-5), 69.5, 75.0, 77.1, 79.3, 81.1, 82.4 (α & β C-2, C-3, C-4), 72.5, 72.8, 73.9, 74.03, 74.3 (3 x α & β CH_2Ph), 90.5 (α C-1), 96.8 (β C-1), 126.9-127.8 (15 x CHPh), 137.1-138.0 (3 x qCPh).

3.6.5.3 2,3,4-Tri-*O*-benzyl-D-*xylo*-1,5-lactone (127)[167]

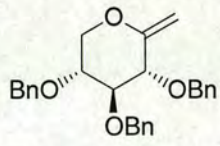
Lab. Book Ref. KG 254
Molecular Formula $C_{26}H_{26}O_5$
Formula Weight 418



The title compound was produced using an identical oxidation method to that employed for the glucose analogue **114**; 2,3,4-tri-*O*-benzyl-α-D-xylopyranose (**126**) (2.30 g, 5.5 mmol) was dissolved in a mixture of acetic anhydride (10 ml) and DMSO (15 ml) that was stirred overnight to give, on work up, the product as a yellow oil (1.81 g, 78%); $[\alpha]_D$ +56.3 (c = 1.42, $CHCl_3$); R_f 0.79 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.98-4.02, 4.19-4.24, 4.39-4.42 (4H, 3 x m, 2-H, 4-H, 5a-H, 5b-H), 4.63 (1H, t, 3-H), 4.76-5.00 (5H, m, CH_2Ph), 5.27 (1H, t, CH_2Ph), 7.58-7.64 (15H, m, Ph); *J*(x-y)/Hz 2-3 7.2, 3-4 7.2, 4-5a nd, 4-5b nd, 5a-5b nd; δ_C (63 MHz, $CDCl_3$) 60.2 (C-5), 68.0, 72.5, 73.5 (3 x CH_2Ph), 75.8, 79.2, 80.7, (C-2, C-3, C-4), 127.3-128.3 (15 x PhCH), 136.7-137.3 (3 x PhC), 169.2 (C-1); ν_{max} (film) 3088, 3063, 3031, 2916, 2869, 1754 and 1216 cm^{-1}.

3.6.5.4 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*xylo*-hex-1-enitol (63)

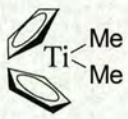
Lab. Book Ref. KG 259
Molecular Formula $C_{27}H_{28}O_4$
Formula Weight 416



The title compound was produced using the same olefination method as that employed for the glucose analogue **59**; 2,3,4-tri-*O*-benzyl-D-*xylo*-1,5-lactone (**127**) (0.48 g, 1.2 mmol) was refluxed in toluene (50 ml) with dimethyl titanocene (**115**) (0.48 g, 2.30 mmol). Work up afforded the title compound as an impure brown oil; R_f 0.49 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$); 3.96-3.98 & 4.17-4.24 (5H, 2 x m, 3-H, 4-H, 5-H, 6a-H, 6b-H), 4.37 (1H, broad s, 1a-H), 4.47 (1H, broad s, 1b-H), 4.65-4.86 (8H, m, CH_2Ph), 7.45-7.57 (15H, m, Ph); *J*(x-y)/Hz 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 66.2 (C-6), 69.9, 71.9, 73.3 (3 x CH_2Ph), 79.9, 80.9, 81.8 (C-3, C-4, C-5), 86.4 (C-1), 125.8-128.8 (15 x CHPh), 137.4-138.1 (3 x qCPh), 159.2 (C-2).

3.6.6 Dicyclopentadienyl-dimethyltitanium (Dimethyl Titanocene) (115)[168]

Lab. Book Ref. KG 193
Molecular Formula $C_{12}H_{16}Ti$
Formula Weight 208



In the absence of light a solution of methyllithium (30 ml, 48 mmol, 1.6M in ether) was carefully added to a cold (10°C) solution of titanocene dichloride (5.04 g, 20.2 mmol) in dry ether (100 ml), under nitrogen. After completion of the addition, the mixture was allowed to warm to room temperature, stirred for a further 10 min, and then cooled to 0-5°C, and at this temperature ice/water (15 ml) was added dropwise to decompose the excess methyllithium. The aqueous phase was extracted with ether (2 x 50 ml), the combined organic layers were dried ($MgSO_4$) and the solvent was *in vacuo* in the dark at 20°C to yield the title complex as orange needles (4.06 g, 97%), dec.p. 93-96°C (lit.[166] 93-96°C).

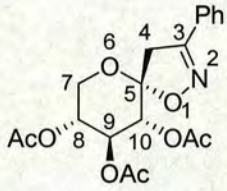
3.7 Cycloaddition Reactions of Exoglycals

3.7.1 General Method for Cycloaddition of Nitrile Oxides to Exoglycals[12,13]

The exoglycal (1 eq.) was dissolved in sodium-dried ether and the nitrile oxide precursor (1.1 eq.) was added with stirring. The solution was cooled (ice bath) and triethylamine (1.2 eq.) in sodium-dried ether was added to the mixture over ~16-48 h using a syringe pump. The solution was then stirred for a further sixteen hours, after which the triethylamine hydrochloride precipitate was removed by filtration to leave the reaction mixture containing

the desired product plus unreacted alkene and the furoxan. The product was purified by chromatography (silica, 0→100% ethyl acetate in petroleum ether; gradient elution).

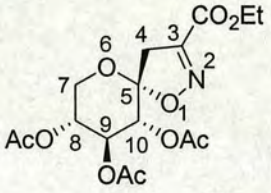
3.7.2 (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (129)



Lab. Book Ref. KG 127
Molecular Formula $C_{19}H_{21}NO_8$
Formula Weight 391

Using the general method described above; triethylamine (230 mg, 2.3 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-D-*xylo*-hex-1-enitol (**62**) (127 mg, 0.53 mmol) and benzohydroximoyl chloride (**68**) (83 mg, 0.53 mmol) in sodium-dried ether (50 ml). The mixture afforded, in order of elution, unreacted alkene (40 mg, 32%) and the title compound that was isolated as a white solid (95 mg, 76%, based on consumed **62**); mp 127-130°C; $[\alpha]_D^{18}$ +32.8 (c = 0.58, $CHCl_3$); R_f 0.51 (Et_2O); δ_H (250 MHz, $CDCl_3$) 2.17, 2.18 (9H, s, CH_3), 3.44 (2H, s, 4-H), 3.99 (1H, dd, 7a-H), 4.08 (1H, t, 7b-H), 5.20 (1H, ddd, 8-H), 5.48 (1H, d, 10-H), 5.68 (1H, t, 9-H), 7.50-7.78 (5H, m, Ph); *J*(x-y)/Hz 7a-7b 11.2, 7a-8 6.4, 7b-8 10.5, 8-9 9.6, 9-10 10.1; δ_C (63 MHz, $CDCl_3$) 20.7, 20.8 (CH_3), 43.4 (C-4), 60.3 (C-7), 69.0, 69.5, 71.2 (C-8, C-9, C-10), 107.2 (C-5), 126.9, 128.9, 130.9 (5 x CHPh), 128.5 (qCPh), 157.8 (C-3), 169.8, 170.1, 170.4 (*C*OCH_3); *m/z*(FAB) Found: M^++1 392.1347. $C_{19}H_{22}NO_8$ requires M^++1 392.1345; Calc. For $C_{19}H_{21}NO_8$: C, 58.31; H, 5.37; N, 3.58. Found: C, 58.28; H, 5.37; N, 3.41%.

3.7.3 (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(acetoxy)-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (130)



Lab. Book Ref. KG 133
Molecular Formula $C_{16}H_{21}NO_{10}$
Formula Weight 387

Using the general method described above; triethylamine (238 mg, 2.35 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-D-*xylo*-hex-1-enitol (**62**) (161 mg, 0.59 mmol) and ethyl chlorooximidoacetate (**67**) (102 mg, 0.67 mmol) in sodium-dried ether (50 ml). Column chromatography gave, in order of

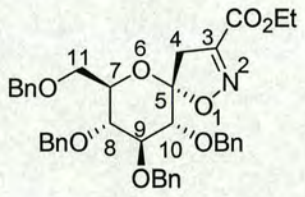
elution, recovered alkene (77 mg, 48%), the title compound, produced as an oil (106 mg, 94%, based on consumed **62**) and diethoxycarbonyl furoxan (35 mg, 23%); $[\alpha]_D^{18}$ +40.3 (c = 0.72, $CHCl_3$); R_f 0.41 (Et_2O); δ_H (250 MHz, $CDCl_3$) 1.30 (3H, t, CH_2CH_3), 1.98, 1.99, 2.00 (9H, 3 x s, $COCH_3$), 3.10 (2H, 2 x s, 4-H), 3.81 (1H, s, 7b-H), 3.84 (1H, s, 7a-H), 4.29 (2H, q, CH_2CH_3), 5.00 (1H, d, 8-H), 5.23 (1H, d, 10-H), 5.45 (1H, t, 9-H); *J*(x-y)/Hz CH_3CH_2 7.1, 7a-7b nd, 7a-8 nd, 7a-8 nd, 8-9 9.6, 9-10 9.0; δ_C (63 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 20.7 x 2 ($COCH_3$), 42.0 (C-4), 60.6 (C-7), 62.6 (CH_2CH_3), 68.6, 69.3, 70.9 (C-8, C-9, C-10), 108.0 (C-5), 152.7 ($CO_2CH_2CH_3$), 159.7 (C-3), 169.8, 169.9, 170.0 ($COCH_3$); *m/z*(FAB) Found: M^++1 388.1242. $C_{16}H_{22}NO_{10}$ requires M^++1 388.1244.

3.7.4 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (132)

Lab. Book Ref. KG 205

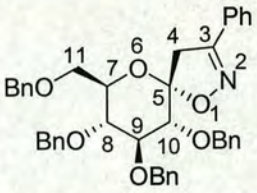
Molecular Formula $C_{39}H_{41}NO_8$

Formula Weight 651



Using the general method described above; triethylamine (108 mg, 1.07 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (198 mg, 0.37 mmol) and ethyl chloro-oximinoacetate (**67**) (70 mg, 0.46 mmol) in sodium-dried ether (50 ml). This resulted in only the title compound being produced as an oil (172 mg, 72 %, based on consumed **59**); $[\alpha]_D^{18}$ +3.2 (c = 1.24, $CHCl_3$); R_f 0.63 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 1.55 (3H, t, CH_2CH_3), 3.15 (1H, d, 4a-H), 3.24 (1H, d, 4b-H), 3.77 (1H, dd, 11a-H), 3.87 (1H, dd, 11b-H), 3.94 (1H, d, 10-H), 4.00 (1H, t, 8-H), 4.26 (1H, dt, 7-H), 4.30 (1H, t, 9-H), 4.51 (2H, q, CH_2CH_3), 4.66-5.19 (8H, m, CH_2Ph), 7.41-7.55 (20H, m, Ph); *J*(x-y)/Hz CH_3CH_2 7.7, 4a-4b 18.4, 7-8 10.2, 7-11a 1.8, 7-11b 2.7, 8-9 9.2, 9-10 9.7, 11a-11b 11.3; δ_C (63 MHz, $CDCl_3$) 13.4 (CH_3), 40.9 (C-4), 61.5 (CH_2CH_3), 67.3 (C-11), 72.2 (C-7), 72.8, 74.3, 74.4, 75.0 (4 x CH_2Ph), 76.8 (C-8), 77.7 (C-10), 83.0 (C-9), 110.3 (C-5), 126.3-127.9 (20 x CHPh), 136.9, 137.1, 137.4, 137.6 (4 x qCPh), 151.9 (CO_2Et), 159.5 (C-3); *m/z*(FAB) Found: M^++1 652.2910. $C_{39}H_{42}NO_8$ requires M^++1 652.2916.

3.7.5 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133)



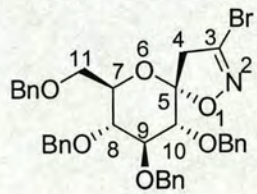
Lab. Book Ref. KG 204

Molecular Formula $C_{42}41_1NO_6$

Formula Weight 655

Using the general method described above; triethylamine (202 mg, 1.99 mmol) dissolved in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (401 mg, 0.75 mmol) and benzohydroximoyl chloride (**68**) (131 mg, 0.84 mmol) in sodium-dried ether (50 ml). Column chromatography gave unreacted exoglycal (35 mg, 9%) with the title compound being produced as a white solid that was recrystallised from ethyl acetate:petroleum ether to give a crystalline solid (422 mg, 94%, based on consumed **59**); mp 127-130°C; $[\alpha]_D^{18}$ –2.2 (c = 1.84, $CHCl_3$); R_f 0.22 (petroleum ether:ethyl acetate, 4:1); δ_H (360 MHz, $CDCl_3$) 3.05 (2H, s, 4-H), 3.58 (1H, dd, 11a-H), 3.74 (1H, d, 10-H), 3.76 (1H, dd, 11b-H), 3.83 (1H, t, 8-H), 4.07 (1H, dt, 7-H), 4.14 (1H, t, 9-H), 4.40-5.00 (8H, m, CH_2Ph), 7.24-7.37 (25H, m, Ph); *J*(x-y)/Hz 7-8 10.1, 7-11a 1.9, 7-11b 2.9, 8-9 9.2, 9-10 9.7, 11a-11b 10.9; δ_C (63 MHz, $CDCl_3$) 42.4 (C-4), 67.4 (C-11), 71.8 (C-7), 72.8, 74.1, 74.3, 75.1 (4 x CH_2Ph), 77.0 (C-8), 77.8 (C-10), 83.4 (C-9), 108.3 (C-5), 126.0-129.6 (25 x CHPh), 137.1, 137.5, 137.7 (5 x qCPh), 157.0 (C-3); *m/z*(FAB) Found: M^++1 656.301. $C_{42}H_{42}NO_6$ requires M^++1 656.2989; Calc. For $C_{42}H_{41}NO_6$: C, 76.95; H, 6.25; N, 2.14. Found: C, 75.26; H, 6.24; N, 2.00%.

3.7.6 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-bromo-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (134)



Lab. Book Ref. KG 206

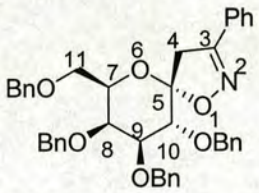
Molecular Formula $C_{36}H_{36}BrNO_6$

Formula Weight 658

Using the general method described above; triethylamine (109 mg, 1.08 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (201 mg, 0.38 mmol) and dibromoformaldoxime (**66**) (90 mg, 0.44 mmol) in sodium-dried ether (50 ml). Column chromatography afforded, in order of elution the title compound being produced as an oil (164 mg, 66%, based on consumed

alkene) and the furoxan as a white solid (33 mg, 31%); $[\alpha]_D^{18}$ +17.4 (c = 1.38, $CHCl_3$); R_f 0.45 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 2.75 (1H, d, 4a-H), 2.86 (1H, d, 4b-H), 3.48-3.75 (4H, m, 8-H, 10-H, 11a-H, 11b-H), 3.87-4.02 (2H, m, 7-H, 9-H), 4.38-4.88 (8H, m, CH_2Ph), 7.05-7.26 (20H, m, Ph); *J*(x-y)/Hz 4a-4b 17.8, 7-8 nd, 7-11a nd, 7-11b nd, 8-9 nd, 9-10 nd, 11a-11b nd; δ_C (63 MHz, $CDCl_3$) 48.2 (C-4), 67.2 (C-11), 72.0 (C-7), 73.8, 74.1, 74.3, 75.1 (4 x *C*H_2Ph), 77.8 (C-8), 82.9 (C-10), 84.0 (C-9), 108.9 (C-5), 127.0-128.0 (20 x CHPh), 136.9-137.7 (4 x qCPh), 155.6 (C-3); *m/z*(FAB) Found: Br^{79} M^++1 658.18042. $C_{36}H_{37}NO_6Br$ requires M^++1 658.1802; Found: Br^{81} M^++1 660.17706 $C_{36}H_{37}NO_6Br$ requires M^++1 660.1785.

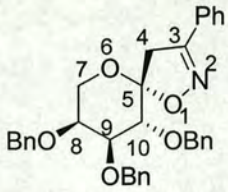
3.7.7 (5*R*,7*S*,8*S*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (135)



Lab. Book Ref. KG 265
Molecular Formula $C_{42}H_{41}NO_6$
Formula Weight 655

Using the general method described above; triethylamine (460 mg, 4.56 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-1-enitol (**65**) (578 mg, 1.08 mmol) and benzohydroximoyl chloride (**68**) (240 mg, 1.54 mmol) in sodium-dried ether (50 ml). This resulted in the title compound being produced as a white solid (579 mg, 82%, based on consumed alkene); mp 136°C; $[\alpha]_D^{18}$ –3.5 (c = 1.14, $CHCl_3$); R_f 0.33 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 3.39 (2H, s, 4-H), 3.99 (1H, dd, 11a-H), 4.07-4.20 (3H, m, 8-H, 10-H, 11b-H), 4.43-4.47 (2H, m, 7-H, 9-H), 4.73-5.34 (8H, m, *C*H_2Ph), 7.57-7.71 (20H, m, Ph); *J*(x-y)/Hz 7-8 nd, 7-11a 1.9, 7-11b nd, 8-9 nd, 9-10 nd, 11a-11b 10.9; δ_C (63 MHz, $CDCl_3$) 42.9 (C-4), 67.9 (C-11), 72.4 (C-7), 73.4, 74.7, 74.8, 75.6 (4 x *C*H_2Ph), 77.6 (C-8), 78.3 (C-10), 83.9 (C-9), 108.8 (C-5), 126.6-130.2 (20 x CHPh), 137.7-138.2 (4 x qCPh), 157.6 (C-3); *m/z*(FAB) Found: M^++1 656.3012. $C_{42}H_{42}NO_6$ requires M^++1 656.3025; Calc. For $C_{42}H_{41}NO_6$: C, 76.92; H, 6.30; N, 2.14. Found: C, 75.99; H, 6.25; N, 2.01%.

3.7.8 (5*R*,8*S*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (136)



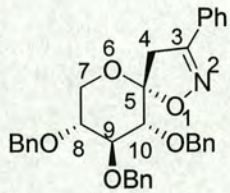
Lab. Book Ref. KG 272

Molecular Formula $C_{34}H_{33}NO_5$

Formula Weight 535

Using the general method described above; triethylamine (450 mg, 3.20 mmol) in sodium-dried ether (50 ml) was added to a solution of 2,6-anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*arabino*-hept-1-enitol (**64**) (497 mg, 1.19 mmol) and benzohydroximoyl chloride (**68**) (238 mg, 1.53 mmol) in sodium-dried ether (50 ml). This resulted in the title compound being produced as a white solid (321 mg, 50%, based on consumed alkene); mp 108-109°C; $[\alpha]_D^{18}$ +5.2 (c = 0.58, $CHCl_3$); R_f 0.35 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 3.17 (1H, d, 4a-H), 3.32 (1H, d, 4b-H), 3.86 (1H, dd, 7a-H), 3.94 (1H, dm, 7b-H), 4.05 (1H, dm, 8-H), 4.17 (1H, dd, 9-H), 4.35 (1H d, 10-H), 4.77-4.87 (5H, m, CH_2Ph), 5.15 (1H, d, CH_2Ph), 7.31-7.47 (20H, m, 4 x Ph); *J*(x-y)/Hz 4a-4b 17.3, 7a-7b 12.9, 7a-8 1.7, 7b-8 1.6, 8-9 3.0, 9-10 10.0; δ_C (63 MHz, $CDCl_3$) 43.0 (C-4), 62.3 (C-7), 71.6, 72.1, 74.7 (3 x *C*H_2Ph), 73.3 (C-8), 75.2 (C-10), 79.7 (C-9), 109.7 (C-5), 126.5-130.1 (20 x CHPh), 138.0 (4 x qCPh), 157.5 (C-3). *m/z*(FAB) Found: M^++1 536.2437. $C_{34}H_{34}NO_5$ requires M^++1 536.2437; Calc. For $C_{34}H_{33}NO_5$: C, 76.24; H, 6.21; N, 2.62. Found: C, 77.09; H, 6.19; N, 2.53%.

3.7.9 (5*R*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (137)



Lab. Book Ref. KG 364

Molecular Formula $C_{34}H_{33}NO_5$

Formula Weight 535

Using the general method above: triethylamine (141 mg, 1.39 mmol) in sodium-dried ether (50 ml) was added to a solution of benzohydroximoyl chloride (**68**) (196 mg, 1.26 mmol) and the crude oil produced in section 3.6.5.4 that contained 2,6-anhydro-3,4,5-tri-*O*-benzyl-1-deoxy-D-*xylo*-hept-1-enitol (**63**) in sodium-dried ether (50 ml). This resulted in the title compound as an oil (88 mg, 14% over 2 steps); $[\alpha]_D^{18}$ +24.0 (c = 0.96, $CHCl_3$); R_f 0.28 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$); 3.68 (2H, s, 4-H), 3.83-3.97 (2H, m, 7a-H, 7b-H), 4.30-4.32 (1H, m, 8-H), 4.59-4.61 (2H, m, 9-H, 10-H), 4.76-4.97 (6H, m,

CH_2Ph), 7.40-7.65 (20H, m, Ph); *J*(x-y)/Hz 7a-7b nd, 7a-8 nd, 7b-8 nd, 8-9 nd, 9-10 nd; δ_C (63 MHz, $CDCl_3$) 43.0 (C-4), 68.0 (C-7), 72.4, 73.6, 74.7 (3 x *C*H_2Ph), 78.3, 77.4, 80.8 (C-8, C-9, C-10), 108.8 (C-5), 126.6-128.3 (20 x CHPh), 136.8, 137.3, 137.7 (4 x qCPh), 157.8 (C-3); *m/z*(FAB) Found: M^++1 536.2433. $C_{34}H_{34}NO_5$ requires M^++1 536.2437.

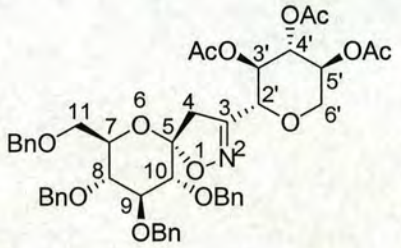
3.7.10 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-(3',4',5'-Tri-*O*-acetyl-β-D-*xylo*-pyran-2'-yl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (144)

3.7.10.1 The Dehydrohalogenation Approach to the D-Xylose Nitrile Oxide (57)

Lab. Book Ref. KG 230

Molecular Formula $C_{47}H_{51}NO_{13}$

Formula Weight 837



2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (97 mg, 0.18 mmol) and hydroximoyl chloride **72** (73 mg, 0.22 mmol) were dissolved in sodium-dried ether (50 ml), the solution was cooled and triethylamine (0.04 ml, 0.29 mmol) in sodium-dried ether (50 ml) was added over 24 h. The resulting suspension was filtered to remove the triethylamine hydrochloride salt and the solvent was removed *in vacuo*, to leave a crude white solid. Column chromatography yielded, in order of elution, unreacted exoglycal **59** (36 mg, 37%), the title compound as a white solid (68 mg, 72%, based on consumed **59**) and the xylose furoxan **145** (20 mg, 15%); **144**; mp 94-98°C; $[\alpha]_D^{18}$ -18.5 (c = 1.46, $CHCl_3$); R_f 0.12 (petroleum ether:ethyl acetate, 4:1); δ_H (360 MHz, $CDCl_3$) 1.84, 1.95, 1.97 (9H, s, CH_3), 2.77 (1H, d, 4a-H), 2.90 (1H, d, 4b-H), 3.29 (1H, t, 6a'-H), 3.47 (1H, dd, 11a-H), 3.57 (1H, d, 10-H), 3.68 (1H, m, 11b-H), 3.72 (1H, t, 8-H), 3.88 (1H, m, 7-H), 3.97 (1H, t, 9-H), 4.17 (1H, dd, 6b'-H), 4.39 (1H, d, 2'-H), 4.50-4.78 (8H, m, CH_2Ph), 4.92 (1H, m, 5'-H), 4.97 (1H, t, 3'-H), 5.15 (1H, t, 4'-H), 7.16-7.25 (20H, m, Ph); *J*(x-y)/Hz 4a-4b 17.7, 7-8 9.4, 7-11a 1.8, 7-11b nd, 8-9 9.2, 9-10 9.7, 11a-11b 11.0, 2'-3' 9.9, 3'-4' 9.5, 4'-5' 9.4, 5'-6a' 10.6, 5'-6b' 5.6, 6a'-6b' 11.3, δ_C (63 MHz, $CDCl_3$) 20.2, 20.5, 20.5 (CO*C*H_3), 41.1 (C-4), 66.7 (C-6'), 68.1 (C-11), 68.7, 68.7 (C-3', C-7), 72.5 (C-4'), 72.9 (C-2'), 73.4, 74.7, 74.7, 75.5 (4 x *C*H_2Ph), 74.1 (C-5'), 77.4 (C-8), 78.3 (C-10), 83.7 (C-9), 108.7 (C-5), 127.5-128.3 (20 x CHPh), 137.5, 137.9, 138.0, 138.2 (4 x qCPh), 156.1 (C-3), 169.0, 169.0, 169.7 (*C*OCH_3); *m/z*(FAB) Found: M^++1 838.3426. $C_{47}H_{52}NO_{13}$requires M^++1 838.3439.

3.7.10.2 The Dehydration Approach to The D-Xylose Nitrile Oxide (57)[5]

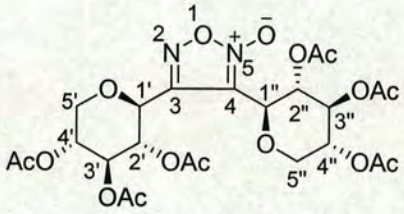
2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (97 mg, 0.18 mmol) and 2,6-anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-β-D-nitromethylxylose (**70**) (58 mg, 0.18 mmol) were dissolved in sodium-dried toluene (25 ml), under nitrogen. Triethylamine (0.1 ml, catalytic) and tolylene 2,4-diisocyanate (0.5 ml, 3.5 mmol) were added to the reaction mixture, which was heated at 109°C for eight days, this resulted in a polymeric solid. The reaction was cooled to 0°C and diaminoethane (≥ 3 eq., 0.1 ml) was slowly added with vigorous stirring. After 1 h the reaction mixture was filtered to remove the polymeric urea and the sinter was washed with chloroform (2 x 50 ml). The combined organics were evaporated to give a crude white solid. Column chromatography resulted, in order of elution, the recovered alkene **59** (23 mg, 24%), the title compound as a white solid **144** (64 mg, 55%, based on consumed **59**) and the furoxan **145** as a crude mixture with some baseline material.

3.7.10.3 3,4-Di-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (145)[124a]

Lab. Book Ref. KG 138

Molecular Formula $C_{24}H_{30}N_2O_{16}$

Formula Weight 602

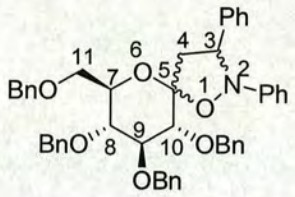


To a stirred solution of 2,6-anhydro-3,4,5-tri-*O*-acetyl-1-deoxy-1-nitroxylose (**70**) (0.192 g, 0.602 mmol) in dry toluene (25 ml), under nitrogen, was added triethylamine (0.1 ml, catalytic) and tolylene 2,4-diisocyanate (3 eq., 0.259 ml). The reaction mixture was heated at reflux for eight days (109°C), over which time a polymeric solid was formed. The reaction was cooled to 0°C and diaminoethane (≥ 3 eq., 0.12 ml) was slowly added with vigorous stirring. After an hour the reaction mixture was filtered to remove the polymeric urea and the sinter was washed with chloroform (2 x 50 ml). The combined organics were evaporated to leave the title compound as a white solid. This was recrystallised from ethanol:hexane to give pure furoxan (121 mg, 67 %); mp 190°C $[\alpha]_D^{18}$ –95.9 (c = 0.44, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.87, 1.89, 1.98, 1.99, 2.00, 2.01 (18H, 6 x s, $COCH_3$), 3.43 (2H, dd, 5'b & 5"b-H), 4.27 (2H, dd, 5'a & 5"a-H), 4.78 (2H, d, 1' & 1"-H), 4.99 (2H, ddd, 4' & 4"-H), 5.29 (2H, dd, 3' & 3"-H), 5.37 (2H, dd, 2' & 2"-H); *J*(x-y)/Hz 1'/1"-2'/2" 2.0, 2'/2"-3'/3" 9.3, 3'/3"-4'/4" 2.5, 4'/4"-5a'/5a" 5.4, 4'/4"-5b'/5b" 10.8, 5a'/5a"-5b'/5b" 7.7; δ_C (63 MHz, $CDCl_3$) 20.24, 20.48, 20.68 ($COCH_3$), 66.98, 67.13 (5'C, 5"C), 68.50 (1'C, 1"C), 69.97, 70.44, 71.78, 72.68 (1'C, 1"C, 2'C, 2"C, 3'C, 3"C, 4'C, 4"C), 112.87 (3C), 153.92 (4C), 169.50,

169.69, 169.85, 170.05, 170.11 ($COCH_3$); *m/z* (FAB) Found: M^++1 603.1684. $C_{24}H_{30}N_2O_{16}$ requires M^++1 603.1674.

3.7.11 (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-2,3-diphenyl-1,6-dioxa-2-azaspiro[4.5]decane (146)[169]

Lab. Book Ref. KG 371
Molecular Formula $C_{43}H_{45}NO_6$
Formula Weight 671

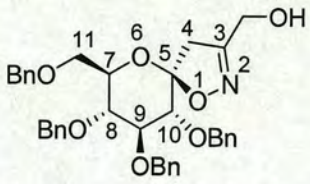


A mixture of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**59**) (496 mg, 0.92 mmol, 1 eq) was refluxed for three days in dry toluene (10 ml) with *N*,α-diphenyl nitrone (363 mg, 1.84 mmol, 2 eq.). The solvent was removed *in vacuo* and the cycloadduct was separated from the residue using dry flash chromatography (silica, 0→100% ethyl acetate in petroleum ether; gradient elution) to give the title compound as two inseparable diastereomers as an oil (619 mg, 56%, based on consumed alkene); $[\alpha]_D^{25}$ +42.0 (c = 1.62, $CHCl_3$); R_f 0.61 (major) 0.56 (minor) (petroleum ether: ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$); 1.87, 1.86 (1H, 2 x s, 4-H, two diastereomers), 3.66-3.90 (4H, m, 10-H, 8-H, 11a-H, 11b-H), 4.13-4.24 (1H, m, 7-H), 4.31-4.40 (1H, m, 9-H), 4.59 (1H, s, 3-H), 4.64-5.05 (8H, m, CH_2Ph), 7.16-7.68 (30H, m, Ph); *J*(x-y)/Hz 3-4a nd, 3-4b nd, 7-11a nd, 7-11b nd, 7-8 nd, 8-9 nd, 9-10 nd, 11a-11b nd; δ_C (63 MHz, $CDCl_3$) 48.0, 53.3 (C-4, two diastereomers), 68.0, 68.3, 70.6, 72.4, 73.2, 73.6, 74.9, 75.3, 75.5 (CH_2Ph, C-11, two diastereomers), 70.0 (C-3), 72.0, 73.6, 74.3, 75.8, 78.2 (C-7, C-8, C-10, two diastereomers), 84.3 (C-9), 104.4 (C-5), 127.4-128.5 (30 x CHPh), 137.6, 137.8, 138.0, 138.1, 138.2 (5 x qCPh), 144.7, 149.7 (qCNPh, two diastereomers); *m/z* (FAB) Found: M^++1 734.3482 $C_{48}H_{48}NO_6$ requires M^++1 734.3489.

3.8 Reactions of Cycloadducts

3.8.1 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-hydroxymethyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (147)[88]

Lab. Book Ref. KG 320
Molecular Formula $C_{37}H_{39}NO_7$
Formula Weight 609



A ten-fold excess of sodium borohydride (297 mg, 7.85 mmol) was added portion-wise to a solution of the ester isoxazoline **132** (511 mg, 0.79 mmol) in ethanol (35 ml). The reaction mixture was stirred at room temperature until the disappearance of the starting material (3-4 h). The solution was then poured into water (25 ml) and extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*, this gave the desired alcohol as a white solid (386 mg, 81%); mp 87-90°C; $[\alpha]_D^{21}$ +2.78 (c = 0.36, $CHCl_3$); R_f 0.03 (petroleum ether:ethyl acetate, 4:1); δ_H (250 MHz, $CDCl_3$) 2.63 (1H, broad s, OH), 2.89 (1H, d, 4a-H), 2.99 (1H, d, 4b-H), 3.71-3.89 (4H, m, 8-H, 10-H, 11a-H, 11b-H) 4.16-4.25 (2H, m, 7-H, 9-H), 4.40 (2H, s, CH_2OH), 4.53-5.12 (8H, m, CH_2Ph), 7.36-7.47 (20H, m, Ph); *J*(x-y)/Hz 4a-4b 17.9, 7-8 nd, 7-11a nd, 7-11b nd, 8-9 nd, 9-10 nd; δ_C (63 MHz, $CDCl_3$) 42.8 (C-4), 57.8 (*C*H_2OH), 67.9 (C-11), 72.2 (C-7), 73.3, 74.7, 74.7, 75.5 (4 x *C*H_2Ph), 77.6, 78.3, 83.8 (C-8, C-9, C-10), 108.6 (C-5), 127.5-128.4 (20 x CHPh), 137.6, 137.6, 138.0, 138.2 (4 x qCPh), 159.7 (C-3); *m/z*(FAB) Found: M^++1 610.2805. $C_{37}H_{39}NO_7$ requires M^++1 610.2799.

3.8.2 Ring Opening Reactions

3.8.2.1 General Procedure for the Hydrogenolysis of Isoxazolines[14]

A mixture of the isoxazoline (1 eq.), boric acid (6 eq.) and the relevant catalyst in methanol:water (5:1; ~15 ml per 100 mg of isoxazoline) and THF. The reaction mixture was degassed, flushed several times with hydrogen, and stirred under hydrogen until the starting material was consumed. After filtration through a celite pad the mixture was concentrated in vacuo (~20°C). Several portions of methanol were added and removed *in vacuo* (to remove the remaining boric acid as trimethyl borate) to yield the product.

Raney Nickel was prepared by repeated washing and decanting with water (x 20), after which the catalyst was stored under methanol in a freezer for 3-4 weeks prior to use.

3.8.2.2 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Palladium/Charcoal

Lab Book Ref. KG 288

Isoxazoline **133** (103 mg, 0.16 mmol) and boric acid (60 mg, 6 eq.) were dissolved in methanol:water (6 ml, 5:1), to this Pd/C catalyst (100 mg) was added. The reaction mixture was degassed three times and left to stir under an atmosphere of hydrogen for 48 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid this afforded a white solid (74 mg, 72%) that was identified as the staring material.

3.8.2.3 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Raney Nickel: Method 1

Lab Book Ref. KG 301

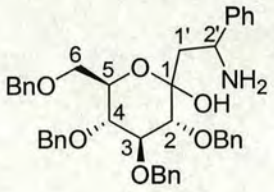
Isoxazoline **133** (54 mg, 0.08 mmol) and boric acid (31 mg, 6 eq.) were dissolved in methanol:water (6 ml, 5:1), to this six spatula tips of Raney nickel catalyst were added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 24 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid this yielded a white solid (24 mg, 44%) that was identified as the staring material.

3.8.2.4 Attempted Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) with Raney Nickel: Method 2

Lab Book Ref. KG 248

Isoxazoline **133** (47 mg, 0.07 mmol) and boric acid (27 mg, 6 eq.) were dissolved in methanol:water (20 ml, 5:1), to this six spatula tips of Raney nickel catalyst were added. Using a Parr high pressure hydrogenator the reaction mixture was degassed three times and was left to stir under a 40 bar atmosphere of hydrogen for 5 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid this yielded a white solid (46 mg, 94%) that was identified as the starting material.

3.8.2.5 Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) Using Pearlman's Catalyst: Method 1



Lab. Book Ref. KG 345

Molecular Formula $C_{42}H_{45}NO_6$

Formula Weight 659

Isoxazoline **133** (147 mg, 0.22 mmol) and boric acid (83 mg, 6 eq.) were dissolved in methanol:water (22 ml, 5:1), to this the palladium hydroxide (Pearlman's) catalyst (100 mg) was added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 24 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid, this yielded an oil that was identified as γ-amino alcohol **149** (141 mg, 95%); $[\alpha]_D^{18}$ = +13.7 (c = 1.9, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.24-4.07 (8H, m, 2'-H, 1a'-H, 1b'-H, 2-H, 3-H, 4-H, 5-H, 6a-H, 6b-H), 4.41-4.55 (4H, m, CH_2Ph), 4.73-4.84 (4H, m, CH_2Ph), 7.08-7.27 (25H, m, Ph); *J*(x-y)/Hz 2'-1a' nd, 2'-1b' nd, 2-3 nd, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd; δ_C (63 MHz, $CDCl_3$) 34.1 (C-1') 50.5, 52.6 (C-2', 2 diastereomers), 68.8 (C-6), 73.2, 74.7, 75.3, 75.6 (4 x CH_2Ph), 70.6, 77.1, 78.4, 83.7 (C-2, C-3, C-4, C-5), 97.7, 98.0, 98.3, 100.7 (C-3', 4 diastereomers), 125.4-129.0 (25 x CHPh), 138.1, 138.2, 138.3, 138.5 (5 x qCPh); δ_C (91 MHz, $CDCl_3$) 34.1, 35.3 (C-1' 2 diastereomers), 50.5, 51.2, 52.3, 52.5 (C-2', 4-diastereomers), 97.7, 98.0, 98.3, 100.7 (C-1, 4 diastereomers), 197.7 (C-3, open chain); *m/z*(FAB) Found: M^++1 660.3320. $C_{42}H_{46}NO_6$ requires M^++1 660.3325.

3.8.2.6 Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (133) Using Pearlman's Catalyst: Method 2

Isoxazoline **133** (142 mg, 0.22 mmol) and boric acid (84 mg, 6 eq.) were dissolved in methanol (22 ml), to this palladium hydroxide (Pearlman's) catalyst (150 mg) was added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 24 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid this yielded an oil that was identified as the title compound in five structural forms ~1:1:1:1:nd (95 mg, 66%).

3.8.2.7 Attempted Reductive Ring Opening of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-carbethoxy-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (132) with Palladium Hydroxide

Lab Book Ref. KG 347

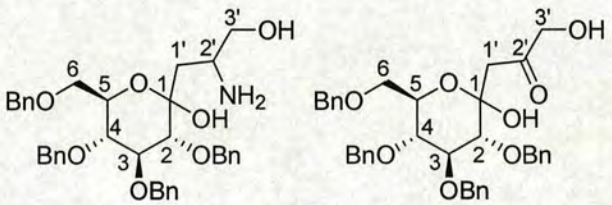
Isoxazoline **132** (88 mg, 0.14 mmol) and boric acid (50 mg, 6 eq.) were dissolved in methanol:water (6 ml, 5:1), to this Pearlman's catalyst (60 mg) was added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 18 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid this yielded an oil (40 mg, 46%) that was identified as the staring material.

3.8.2.8 Hydrogenolysis of (5*R*,7*S*,8*R*,9*S*,10*R*)-8,9,10-Tris(benzyloxy)-7-benzyloxymethyl-3-hydroxymethyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene (147) Using Pearlman's Catalyst

Lab. Book Ref. KG 354

Molecular Formula $C_{37}H_{43}NO_7$

Formula Weight 613



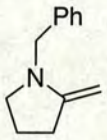
Isoxazoline **147** (130 mg, 0.21 mmol) and boric acid (85 mg, 6 eq.) were dissolved in methanol:water (22 ml, 5:1), to this palladium hydroxide (Pearlman's) catalyst (150 mg) was added. The reaction mixture was degassed three times and was left to stir under an atmosphere of hydrogen for 24 h. The mixture was filtered through a celite pad and the solvent removed *in vacuo*. The resulting solid was co-evaporated with methanol to remove the residual boric acid, this yielded an oil that was identified as a mixture of β-hydroxy ketone **151** and γ-amino alcohol **152** (117 mg, 89%); $[\alpha]_D^{18}$ = +24.4 (c = 2.3, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 3.56-4.65 (10H, m, 1a'-H, 1b'-H, 2'-H, 3a'-H, 3b'-H, 2-H, 3-H, 4-H, 5-H, 6a-H, 6b-H), 4.76-5.28 (8H, m, CH_2Ph), 7.46-7.69 (20H, m, Ph); *J*(x-y)/Hz 1a-1a nd, 1a-2 nd 1b-2 nd, 2-3a nd, 2-3b nd, 5-6 nd, 6-7 nd, 7-8 nd, 8-9a nd, 8-9b nd; δ_C (63 MHz, $CDCl_3$) 29.6, 30.6 (C-1'), 50.2, 50.3 (C-2', 2 diastereomers), 68.4 (C-3'), 69.5(C-8), 73.2, 74.7, 75.1, 75.5 (CH_2Ph), 78.0, 81.4, 82.9, 71.0 (C-2, C-3, C-4, C-5), 97.6 (C-1), 127.6-128.2 (20 x CHPh), 137.6, 137.8, 138.2 (4 x qCPh); δ_C (91 MHz, $CDCl_3$) 210.3 (C-3, open chain); *m/z*(FAB) 596 (M^++1-OH) β-hydroxy ketone, 597 (M^++1-OH) γ-amino alcohol.

3.9 Iminosugars

3.9.1 Synthesis of 5-(*N*-Benzyl-2-pyrrolidine)-3-phenyl-2-isoxazoline (159)

3.9.1.1 *N*-Benzyl-2-methylenepyrrolidine (153)[96]

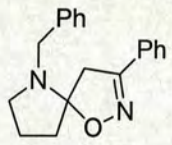
Lab. Book Ref. KG 299
Molecular Formula $C_{12}H_{15}N$
Formula Weight 173



N-Benzyl-2-pyrrolidone (499 mg, 2.85 mmol) was dissolved in sodium-dried toluene (50 ml) with the Petasis reagent (**115**) (1.19 g, 5.7 mmol), the reaction mixture was heated at 70°C for 24 h. The solvent was removed to afford the title compound as an oil, contaminated with titanocene by-products, which was taken on to the next stage without further purification; δ_H (200 MHz, $CDCl_3$) 2.15 (2H, m, 4a-H, 4b-H), 2.60 (2H, t, 3a-H, 3b-H), 3.40 (2H, t, 5a-H, 5b-H), 4.39 (2H, 2 x s, 1a-H, 1b-H), 4.60 (2H, s, CH_2Ph), 7.40 (5H, m, Ph).

3.9.1.2 6-Benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene (159)

Lab. Book Ref. KG 299
Molecular Formula $C_{19}H_{20}N_2O$
Formula Weight 292

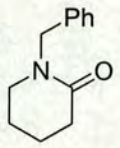


N-Benzyl-2-methylenepyrrolidine (**165**) and benzohydroximoyl chloride (**68**) (0.49 g, 3.13 mmol) were dissolved in sodium-dried ether (50 ml) and triethylamine (0.35 g, 3.45 mmol), in dry ether (50 ml) was added over 24 h using a syring pump. Removal of the solvent *in vacuo* yielded an oil that on column chromatography afforded the product as a brown gum (196 mg, 24% over two steps); R_f 0.41 (ethyl acetate:petroleum ether, 1:4); $[\alpha]_D^{25}$ 0 (c = 1.82, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.98-2.25 (2H, m, 7a-H, 7b-H), 2.60-2.72 (2H, m, 8a-H, 8b-H), 3.00-3.09 (1H, m, 9a-H), 3.21-3.26 (1H, m, 9b-H), 3.52 (1H, d, 4a-H), 3.65 (1H, d, 4b-H), 3.79 (1H, d, CH_2Ph), 4.57 (1H, d, CH_2Ph), 7.43-7.91 (10H, m, Ph); *J*(x-y)/Hz CH_2 14.0, 4a-4b 17.9, 7-7 nd, 7-8 nd, 8-8 nd, 8-9 nd, 9-9 nd; δ_C (63 MHz, $CDCl_3$) 20.3 (C-8), 38.1 (C-9), 40.0 (C-4), 50.6 (C-7, *C*H_2Ph), 107.4, 108.3 (C-5), 126.1-129.6 (10 x CHPh), 139.0 (2 x qCPh), 155.6, 157.7 (C-3); *m/z* (FAB) Found: M^++1 293.1654. $C_{19}H_{21}N_2O$ requires M^++1 293.1654.

3.9.2 Synthesis of 5-(*N*-Benzyl-piperidine)-3-phenyl-2-isoxazoline (160)

3.9.2.1 *N*-Benzyl-2-piperidone (155)[131]

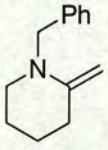
Lab. Book Ref. KG 291
Molecular Formula $C_{12}H_{15}NO$
Formula Weight 189.70



Sodium hydride dispersion in oil (60%, 2.10 g, 48.0 mmol) was washed with anhydrous hexane (3 x 10 ml) under nitrogen, resuspended in dry THF (50 ml), and cooled to 0°C. A solution of δ-valerolactam (4.66 g, 45.5 mmol) in dry THF (200 ml) was slowly added to the suspension. The mixture was stirred at 0°C for 30 min, and at room temperature until cessation of hydrogen evolution. Benzyl chloride (95.2 ml, 45.4 mmol) was added dropwise under nitrogen, and the new mixture was refluxed until completion of the alkylation was observed by tlc (48 h). The reaction was quenched with H_2O (200 ml) the aqueous phase was extracted with Et_2O (100 ml) and CH_2Cl_2 (100 ml). The combined organics were dried ($MgSO_4$), and the remaining benzyl chloride and solvent were removed *in vacuo* to give the title compound (5.73 g, 63%) as a pale oil that was reacted without further purification. R_f 0.14 (petroleum ether:ethyl acetate, 2:1); δ_H (250 MHz, $CDCl_3$) 1.78-1.94 (4H, m, 4-H, 5-H), 2.54-2.59 (2H, m, 6-H), 3.26-3.28 (2H, m, 3-H), 4.69 (2H, s, CH_2Ph), 7.33-7.56 (5H, m, Ph); *J*(x-y)/Hz 3-3 nd, 3-4 nd, 4-4 nd, 4-5 nd, 5-5, nd 5-6 nd, 6-6 nd; δ_C (63 MHz, $CDCl_3$) 21.2 (C-5), 23.0 (C-4), 32.3 (C-3), 47.1 (C-6), 49.9 (*C*H_2Ph), 127.1, 127.9, 128.4 (5 x CHPh), 137.1 (qCPh), 169.7 (C-1); *m/z* (FAB) Found: M^++1 190.12132 $C_{12}H_{16}NO$ requires M^++1 190.1232.

3.9.2.2 *N*-Benzyl-2-methylenepiperidine (154)

Lab. Book Ref. KG 306A
Molecular Formula $C_{13}H_{17}N$
Formula Weight 187

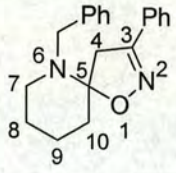


N-Benzyl-2-piperidone (**155**) (250 mg, 1.43 mmol) and the Petasis reagent (**115**) (0.59 g, 2.85 mmol) were dissolved in sodium-dried toluene, the reaction mixture was heated for 24 h at 70°C. The solvent was removed *in vacuo* to yield the product as an oil, which was contaminated with titanocene by-products, but was taken on to the next stage without further

purification; δ_H (200 MHz, $CDCl_3$) 1.90 (4H, m, 4a-H, 4b-H, 5a-H, 5b-H), 3.10 (2H, m, 6a-H, 6b-H), 3.30 (2H, m, 3a-H, 3b-H), 4.30 (2H, s, 1a-H, 1b-H), 4.74 (2H, s, CH_2Ph), 7.30 (5H, m, Ph).

3.9.2.3 6-Benzyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (160)

Lab. Book Ref. KG 306
Molecular Formula $C_{20}H_{22}N_2O$
Formula Weight 306

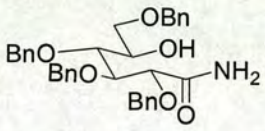


The title compound was produced by the addition of triethylamine (0.24 ml, 1.60 mmol) to a solution of *N*-benzyl-2-methylenepiperidine (**154**) and benzohydroximoyl chloride (**68**) (244 mg, 1.57 mmol) dissolved in dry ether, over 24 h. Concentration and column chromatography afforded the product as a brown solid (72 mg, 23% over two steps); mp 88-91°C; R_f 0.41 (petroleum ether:ethyl acetate, 4:1); $[\alpha]_D^{25}$ 0 (c = 0.94, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.96-2.02 (2H, m, 7a-H, 7b-H), 2.56-2.60 (4H, m, 9a-H, 9b-H, 8a-H, 8 b-H), 3.23 (1H, d, 4a-H), 3.33 (1H, d, 4b-H), 3.60 (1H, d, *C*H_2Ph), 3.83 (1H, d, *C*H_2Ph), 4.45 (1H, d, *C*H_2Ph), 7.25-7.32 (10H, m, Ph); *J*(x-y)/Hz 4a-4b 18.0, 6-6 nd, 6-7 nd, 7-7 nd, 7-8 nd, 8-8 nd, 8-9 nd, 9-9 nd, 9-10 nd, 10-10 nd; δ_C (63 MHz, $CDCl_3$) 38.1 (C-4), 43.8, 45.3, 45.3, 47.7 (C-7, C-8, C-9, C-10), 53.4 (*C*H_2Ph), 101.2 (C-5), 126.1-130.0 (10 x CHPh), 139.3, 140.0 (2 x qCPh), 155.0 (C-3); *m/z* (FAB) Found: M^++1 307.1818. $C_{20}H_{22}N_2O$ requires M^++1 307.1810.

3.9.3 Synthesis of (5*R*,7*S*,8*R*,9*S*,10*R*)-*N*-Boc-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (186)

3.9.3.1 2,3,4,6-Tetra-*O*-benzyl-D-gluconamide (179)[36]

Lab. Book Ref. KG 342
Molecular Formula $C_{34}H_{36}NO_6$
Molecular Weight 555

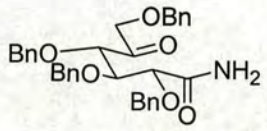


Gluconolactone **114** (2.00 g, 3.7 mmol) was dissolved in 50 ml of an 8N ammonia-solution in methanol. After stirring for 1.5 h, under nitrogen, the reaction mixture was concentrated *in vacuo*. Crystallisation of the yellow oil from ethyl acetate and petroleum ether 60-80

afforded the title compound as white crystals (1.78 g, 86%); mp 75°C (Lit.[168] 89-90°C); R_f 0.22 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.60 (1H, s, OH), 3.69-375 (2H, m, 6aH, 6b-H), 3.80-3.82 (2H, m, 4H, 5-H), 4.13-4.20 (1H, m, 3-H), 4.62-4.69 (1H, m, 2-H), 4.87-5.09 (8H, m, CH_2Ph), 7.42-7.52 (20H, m, Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 68.8 (C-6), 73.0, 73.3, 74.8, 75.5 (4 x CH_2Ph), 77.7, 79.9, 81.5 (C-2, C-3, C-4), 90.9 (C-5), 127.4-128.2 (20 x CHPh), 137.6, 138.3, 138.5 (4 x qCPh), 173.1 (C-1); *m/z*(FAB): Found M^++1 556.2699. $C_{34}H_{38}NO_6$ requires M^++1 556.2699.

3.9.3.2 2,3,4,6-Tetra-*O*-benzyl-5-dehydro-oxo-D-gluconamide (180)[36]

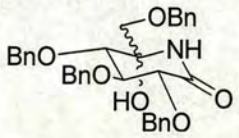
Lab. Book Ref. KG 344
Molecular Formula $C_{34}H_{35}NO_6$
Molecular Weight 554



A solution of **179** (1.93 g, 3.5 mmol) in dimethyl sulphoxide (12.5 ml) and acetic anhydride (7.5 ml) was stirred, under nitrogen, for 12 h. Water (50 ml) was added and the mixture was stirred for a further 15 min, during which time a yellow oil was precipitated. The reaction mixture was extracted with DCM (3 x 30 ml) the combined organics were then washed with water (3 x 30 ml) and brine (2 x 30 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The title compound was carried forward to the next reaction without further purification; R_f 0.26 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.67-3.71 (2H, m, 6a-H, 6b-H), 3.90-3.96 (2H, m, 3H, 4-H), 4.10-4.13 (1H, m, 2-H), 4.44-5.01 (8H, m, CH_2Ph), 7.19-7.37 (20H, m, Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 68.1 (C-6), 73.4, 73.6, 73.8, 73.8 (4 x CH_2Ph), 77.4, 78.0, 80.8 (C-2, C-3, C-4), 127.7-128.3 (20 x CHPh), 136.8, 137.3, 137.4 (4 x qCPh), 169.2 (C-1,C-5).

3.9.3.3 2,3,4,6-Tetra-*O*-benzyl-5-dehydro-5-hydroxy-D-glucono- and L-idonolactam (181)[36]

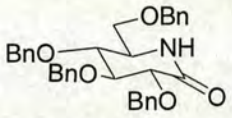
Lab. Book Ref. KG 357
Molecular Formula $C_{34}H_{36}NO_6$
Molecular Weight 554



Compound **180** (267 mg, 0.48 mmol) was dissolved in 10 ml of a solution of ammonia in methanol (8N ammonia). The mixture was stirred for 2 h, after which it was concentrated *in vacuo*. The residue was purified by dry flash chromatography (petroleum ether:ethyl acetate, 2:1). This yielded two products: a white solid identified as **181a** (122 mg, 46%) and a yellow syrup **181b** (139 mg, 52%); **181a** mp 97°C (lit.[36] 99-101°C); R_f 0.14 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.27 (1H, d, 6a-H), 3.34 (1H, d, 6b-H), 3.75 (1H, d, 4-H), 4.01 (1H, d, 2-H), 4.23 (1H, dd, 3-H), 4.41-4.92, (7H, m, CH_2Ph), 5.17 (1H, d, J_{CH2} 11.2, CH_2Ph), 6.29 (1H, broad s, NH), 7.19-7.33 (20H, m, Ph); *J*(x-y)/Hz 2-3 8.6, 3-4 9.6, 6a-6b 9.6; δ_C (63 MHz, $CDCl_3$) 72.3, 73.4, 74.6, 75.1 (4 x CH_2Ph), 75.1 (C-6), 77.1, 79.2, 81.7 (C-2, C-3, C-4), 127.6-128.4 (20 x CHPh), 136.8, 137.1, 137.6, 138.0 (4 x qCPh), 170.6 (C-1), 171.32 (C-5); **181b** R_f 0.06 (ethyl acetate:petroleum ether, 1:1); δ_H (250 MHz, $CDCl_3$) 3.18 (1H, broad s, OH), 3.60-3.68 (2H, m, 6a-H, 6b-H), 3.88-3.93 (2H, m, 3-H, 4-H), 4.25 (1H, d, 2-H), 6.71 (1H, broad s, NH), 7.20-7.33 (20H, m, Ph); *J*(x-y)/Hz 1-2 nd, 2-3 3.4, 4-5 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 70.9, 73.1, 73.5, 73.91 (CH_2Ph), 75.03 (C-6), 77.5, 79.4, 80.4 (C-2, C-3, C-4), 127.5-128.4 (20 x CHPh), 136.6-138.0 (4 x qCPh), 170.4 (C-1), 173.9 (C-5).

3.9.3.4 2,3,4,6-Tetra-*O*-benzyl-D-glucono-δ-lactam (182)[36]

Lab. Book Ref. KG 361
Molecular Formula $C_{34}H_{35}NO_5$
Molecular Weight 537



Compounds **181a** & **181b** (1.00 g, 1.8 mmol) were dissolved in 25 ml acetonitrile and 6.5 ml formic acid. To this mixture, sodium cyanoborohydride (360 mg) was added and the reaction mixture was refluxed for 2 h. The mixture was then cooled in ice and the reaction was quenched by adding aq. hydrochloric acid (0.1M). After stirring for 15 min, the mixture was poured into a solution of ethyl acetate and saturated sodium bicarbonate solution (1:1, 100 ml). The water layer was separated and extracted with ethyl acetate (2 x 50 ml), the combined organic layers were then washed with brine (50 ml), dried ($MgSO_4$), the solvent was removed *in vacuo* and the resulting white solid was recrystallised from petroleum ether:ethyl acetate to give the title compound as white crystals (698 mg, 72%); mp 98°C (lit.[36] 100-102°C); R_f 0.43 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 3.27-3.29 (1H, m, 6a-H), 3.54-3.60 (2H, m, 5-H, 6b-H), 3.67-3.71 (1H, m, 4-H), 3.90-3.99 (2H, m, 2-H, 3-H), 4.44-5.18 (8H, m, CH_2Ph), 6.21 (1H, broad s, NH), 7.78-7.42 (20H, m, Ph);

J(x-y)/Hz 2-3 nd, 3-4 nd, 5-6a nd, 5-6b nd, 6a-6b nd; δ_C (63 MHz, $CDCl_3$) 69.7, 73.2, 75.6, 74.5, 74.5 (C-6, 4 x CH_2Ph), 78.0, 78.6, 80.8, 82.1 (C-2, C-3, C-4, C-5), 127.7-128.3 (20 x Ph), 137.1, 137.4, 137.6, 137.8 (4 x qCPh), 170.6 (C-1); *m/z*(FAB): Found M^++1 538.2598. $C_{34}H_{36}NO_5$ requires M^++1 538.2594.

3.9.3.5 Attempted Synthesis of Pentabenzyl-D-nojirilactam (183) and (5*S*, 6*R*)-N-Benzyl-3,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-1,2,5,6-tetrahydropyridin-2-one (184)[132]

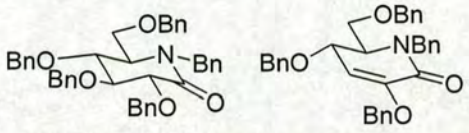
Lab. Book Ref. KG 362

Molecular Formula **183** $C_{41}H_{41}NO_5$

Molecular Formula **184** $C_{34}H_{33}NO_4$

Molecular Weight **183** 627

Molecular Weight **184** 519



The lactam **182** (105 mg, 0.20 mmol) was added to a stirred suspension of freshly pulverised potassium hydroxide (21.9 mg, 0.4 mmol) in dry DMSO (3.9 ml) at room temperature, treated with benzyl chloride (90 ml, 0.78 mmol) for 5 min, and poured into a mixture of saturated sodium bicarbonate solution (2 ml) and diethyl ether (20 ml). The organic layer was separated, and the aqueous layer was extracted with ether (2 x 10 ml) and ethyl acetate (10 ml). The combined organics were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting oil was purified by column chromatography (silica, 0→100% ethyl acetate in petroleum ether, gradient elution) to yield a white solid (43 mg, 42%) that was identified as starting material, a colourless oil R_f 0.59 (hexane:ether, 1:2) (17 mg, 14%) this was thought to be the desired nojirilactam and a brown oil R_f 0.12 (hexane:ether, 1:2) (8 mg, 8%) this was thought to be the side product.

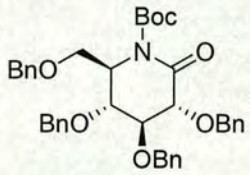
3.9.3.6 Attempted Synthesis of *N*-Benzyloxycarbonyl-2,3,4,6-tetra-*O*-benzyl-D-glucono-δ-lactam (185)[170]

To a stirred, ice-cold, solution of iminosugar **182** (577 mg, 1.07 mmol) in chloroform (25 ml) were added sequentially, triethylamine (1 ml) and benzyloxycarbonyl succinimide (1.02 g, 3.85 mmol). The reaction mixture was allowed to return to room temperature and stirred for 18 h. The solution was washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to leave a white solid. This solid was purified (silica, 0→100% ethyl acetate in

petroleum ether, gradient elution) to give the iminosugar **182** and CbzOSuc as an inseparable mixture.

3.9.3.7 *N*-Boc-2,3,4,6-tetra-*O*-benzyl-D-glucono-δ-lactam (178)[137]

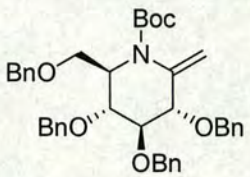
Lab. Book Ref. KG 385
Molecular Formula $C_{39}H_{43}NO_7$
Formula Weight 637



A solution of lactam **182** (232 mg, 0.43 mmol) and DMAP (16 mg, 0.13 mmol) in acetonitrile (7 ml) was treated with Boc_2O (200 mg, 0.92 mmol) and stirred for 5.5 h. The solvent was removed and the resulting oil was purified by column chromatography (silica, 0→100% diethyl ether in hexane, gradient elution) to give the title compound as a yellow oil (164 mg, 46%); R_f 0.32 (petroleum ether:ethyl acetate, 4:1); R_f 0.63 (diethyl ether:hexane, 2:1); $[\alpha]_D^{25}$ +13.8 (c = 0.8, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.65 (9H, s, CMe_3), 3.63 (1H, dd, 6a-H), 3.76 (1H, dd, 6b-H), 3.98-4.07 (2H, m, 3-H, 4-H), 4.33-5.23 (10H, m, CH_2Ph, 2-H, 5-H), 7.35-7.60 (20H, m, Ph); *J*(x-y)/Hz 2-3 nd, 3-4 nd, 4-5 nd, 5-6a 4.85, 5-6b 6.07, 6a-6b 9.68; δ_C (63 MHz, $CDCl_3$) 27.8 ($C(CH_3)_3$), 57.6 (C-5), 69.4 (C-6), 71.5, 73.1, 73.4, 73.9 (4 x CH_2Ph), 76.0, 79.5, 81.7 (C-2, C-3, C-4), 83.5 ($C(CH_3)_3$), 127.5-128.3 (20 x CHPh), 137.4, 137.8 (4 x qCPh), 151.9 (NCO_2CMe_3), 169.4 (C-1); *m/z* (FAB) 1298 (2 M + Na), 638 (M^++ 1), 538, 536 (M^++1-Boc).

3.9.3.8 *N*-boc-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-6-aza-D-*gluco*-hept-1-enitol (60)

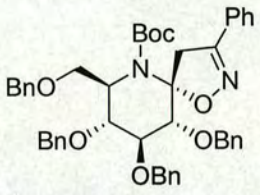
Lab. Book Ref. KG 388
Molecular Formula $C_{40}H_{43}NO_6$
Formula Weight 635



N-Boc-3,4,5,7-tetra-D-*O*-benzyl-δ-glucolactam (**178**) (290 mg, 0.46 mmol, 1 eq.) was dissolved in sodium-dried ether (50 ml) with the Petasis reagent, (**115**) (2 eq.), the reaction mixture was heated at 70°C for 24 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography to afford the title compound as a white solid (15 mg, 8%); mp 63-64°C; R_f 0.45 (petroleum ether:ethyl acetate, 4:1); $[\alpha]_D^{25}$ +40.0 (c = 0.3, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 3.60-3.72 (5H, m, 4-H, 5-H, 6-H, 7a-H, 7b-H),

3.89 (1H, d, 3-H), 4.41-4.82 (10H, m, CH_2Ph, 1a-H, 1b-H), 7.00-7.29 (20H, m, Ph); *J*(x-y)/Hz 1a-1b nd, 3-4 7.22, 4-5 nd, 5-6 nd, 6-7a nd, 6-7b nd.

3.9.3.9 (5*R*,7*S*,8*R*,9*S*,10*R*)-*N*-Boc-8,9,10-tris(benzyloxy)-7-benzyloxymethyl-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-ene (186)



Lab. Book Ref. KG 392

Molecular Formula $C_{47}H_{50}N_2O_7$

Formula Weight 754

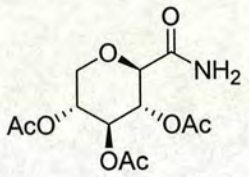
Triethylamine (0.30 ml, 3.0 mmol) in sodium-dried ether (50 ml) was added to a mixture of *N*-Boc-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-6-aza-D-*gluco*-hept-1-enitol (**60**) and benzohydroximoyl chloride (**68**) (222 mg, 1.43 mmol) in sodium-dried ether (50 ml). The reaction mixture was filtered and the solvent removed *in vacuo* and the residue was purified by column chromatography to yield, in order of elution, an unidentified oil (273 mg) and the product as a white solid (35 mg, 3% over two steps); R_f 0.14 (petroleum ether:ethyl acetate, 4:1); $[\alpha]_D$ –7.1 (c = 0.7, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 1.31 (9H, s, CMe_3), 3.12 (2H, s, 4-H), 3.60 (1H, dd, 11a-H), 3.75 (1H, d, 10-H), 3.79 (1H, dd, 11b-H), 3.84 (1H, t, 8-H), 4.08 (1H, dt, 7-H), 4.15 (1H, t, 9-H), 4.48-5.07 (8H, m, CH_2Ph), 7.21-7.45 (25H, m, Ph); *J*(x-y)/Hz 7-8 9.8, 7-11a 1.9, 7-11b 2.9, 8-9 9.5, 9-10 9.7, 11a-11b 10.9; *m/z* (FAB) Found: M^++1 755.3691. $C_{47}H_{51}N_2O_7$ requires M^++1 755.3696, 654 (M^++1 –Boc).

3.10 Nitrile Sulfide Chemistry

3.10.1 Synthesis of 5-(2',3',4'-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (203)

3.10.1.1 *C*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)formamide (206)[143]

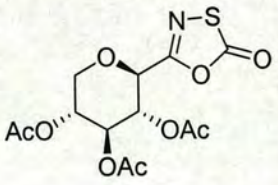
Lab. Book Ref. KG 184
Molecular Formula $C_{12}H_{17}NO_8$
Formula Weight 303



2,3,4-Tri-*O*-acetyl-β-D-xylopyranosylnitrile (**107**) (1.71 g, 6.0 mmol, 1 eq.) was dissolved in glacial acetic acid (5 ml) under nitrogen and the solution was cooled in an ice bath. Titanium tetrachloride (0.13 ml, 0.75 mmol, 0.13 eq.) was added to the solution this was followed by water (0.11 ml, 1 eq.). After 30 min the ice bath was removed, and the mixture was stirred for 5 days at room temperature. The solution was poured into stirred ice-water (50 ml) and then extracted into chloroform (3 x 50 ml). The combined organics were washed with cold sat. $NaHCO_3$ (3 x 50 ml) followed by water (50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting solid was recrystallised from chloroform/diethyl ether, this afforded the product (722 mg, 67%); mp 175°C; R_f 0.03 (petroleum ether:EtOAc, 1:1); $[\alpha]_D^{18}$ –38.0 (c = 1.00, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.13, 2.14, 2.16 (9H, 3 x s, CH_3), 3.48 (1H, dd, 6a-H), 3.93 (1H, d, 2-H), 4.30 (1H, dd, 6b-H), 5.08 (1H, ddd, 5-H), 5.22 (1H, t, 3-H), 5.36 (1H, t, 4-H), 6.28 (1H, broad s, NH), 6.54 (1H, broad s, NH); *J*(x-y)/Hz 2-3 9.6, 3-4 9.3, 4-5 9.2, 5-6a 10.3, 5-6b 5.5, 6a-6b 11.3; δ_C (63 MHz, $CDCl_3$) 21.0 (3 x CH_3), 66.5 (C-6), 69.1, 69.7, 72.9, 76.9 (C-2, C-3, C-4, C-5), 170.2, 170.3, 170.4 (3 x $COCH_3$, C-1); *m/z*(FAB) Found: M^++1 304.1027. $C_{12}H_{18}NO_8$ requires M^++1 304.1032; Calc. For $C_{12}H_{17}NO_8$: C, 47.53; H, 5.65; N, 4.62. Found: C, 47.37; H, 5.60; N, 4.34%.

3.10.1.2 5-(2',3',4'-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (203)[55,56]

Lab. Book Ref. KG 208
Molecular formula $C_{13}H_{15}NO_9S$
Formula Weight 361

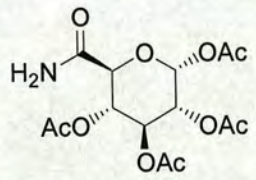


2,3,4-Tri-*O*-acetyl-β-D-xylopyranosylformamide (**206**) (117 mg, 0.39 mmol, 1 eq.) was dissolved in dry chloroform (10 ml) under nitrogen in a flask fitted with an HCl trap. Chlorocarbonylsulfenyl chloride (0.08 ml, 0.94 mmol, 2.42 eq.) was added and the mixture was refluxed vigorously until the reaction was complete by tlc (48 h). The solvent was removed *in vacuo* and the resulting solution was co-evaporated with toluene (3 x 20 ml) to give a brown solid. The solid was dissolved in DCM (50 ml) and purified by filtration through a thin silica pad (5 mm) to give the desired product as a white crystalline solid (104 mg, 74%); mp 134-137°C; R_f 0.49 (ethyl acetate:petroleum ether, 1:1); $[\alpha]_D^{18}$ -41.7 (c = 0.48, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.95, 1.98, 1.99 (9H, 3 x s, CH_3), 3.36 (1H, dd, 5a'-H), 4.20 (1H, dd, 5b'-H), 4.25 (1H, d, 1'-H), 5.00 (1H, ddd, 4'-H), 5.16 (1H, t, 2'-H), 5.22 (1H, t, 3'-H); *J*(x-y)/Hz 1'-2' 9.3, 2'-3' 9.2, 3'-4' 9.2, 4'-5a' 10.7, 4'-5b' 5.5, 5a'-5b' 11.4; δ_C (63 MHz, $CDCl_3$) 20.3, 20.5 x 2 (3 x CH_3), 66.8 (C-5'), 68.1, 69.1, 72.0, 74.5 (C-1', C-2', C-3', C-4'), 155.4 (C-5), 169.3, 169.5, 169.9 (3 x $COCH_3$), 172.2 (C-2); *m/z*(FAB) Found: M^++1 362.0546. $C_{12}H_{16}NO_9S$ requires M^++1 362.0547; Calc. For $C_{13}H_{15}NO_9S$: C, 43.21; H, 4.18; N, 3.88. Found: C, 43.40; H, 4.20; N, 3.71%.

3.10.2 Synthesis of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5-yl)-1,3,4-oxathiazol-2-one (204)

3.10.2.1 *C*-(1,2,3,4-Tetra-*O*-acetyl-*α*-D-*gluco*-pentopyranos-5-yl)formamide (207)[171]

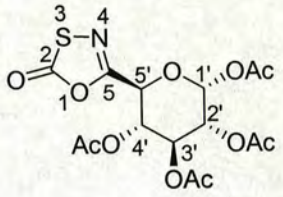
Lab. Book Ref. KG 333a
Molecular Formula $C_{14}H_{19}NO_{10}$
Formula Weight 361



Acetic anhydride (20 ml) was added to a suspension of glucuronamide (2.00 g, 10.4 mmol) in pyridine (20 ml), and the reaction mixture left stirring overnight, under nitrogen, at room temperature. The mixture was concentrated *in vacuo*, azeotroped with toluene followed by diethyl ether. The product recrystallised from ethanol to give the title compound as small colourless crystals (3.424 g, 92%); mp 155-156°C; R_f 0.12 (petroleum ether:ethyl acetate, 1:1); $[\alpha]_D^{18}$ = +10.4 (c = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.40, 2.19, 2.19 (12H, 4 x s, $COCH_3$), 4.40 (1H, d, 5-H), 5.19 (1H, dd, 2-H), 5.34 (1H, dd, 4-H), 5.64 (1H, t, 3-H), 6.02 (1H, broad s, $CONH_2$), 6.48 (1H, d, 1-H), 6.55 (1H, broad s, $CONH_2$); *J*(x-y)/Hz 1-2 3.6, 2-3 10.1, 3-4 9.6, 4-5 10.1; δ_C (63 MHz, $CDCl_3$) 20.3, 20.5, 20.6 (4 x $COCH_3$), 68.8, 70.1 (C-1,

C-2, C-3, C-4), 88.1 (C-5), 168.7, 168.9, 169.6, 169.7 (4 x *C*$COCH_3$, *C*$CONH_2$); *m/z*(FAB) Found: M^++1 362.1086. $C_{14}H_{20}NO_{10}$ requires M^++1 362.1087.

3.10.2.2 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (204)

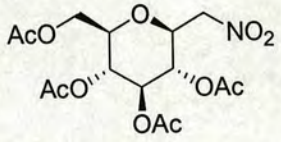


Lab. Book Ref. KG 333
Molecular Formula $C_{15}H_{17}NO_{11}S$
Formula Weight 419

Chlorocarbonylsulfenyl chloride (0.1 ml, 1.2 mmol, 4.2 eq.) was added to a solution of amide **207** (100 mg, 0.28 mmol) in Na-dried toluene (3 ml), and the mixture heated at reflux for 6 h. The reaction mixture was concentrated, azeotroped with toluene and recrystallised twice from ethyl acetate to give the title compound as small colourless crystals (92 mg, 82%); mp 212-214°C; R_f 0.82 (petroleum ether:ethyl acetate, 1:1); $[\alpha]_D^{18}$ = + 12.7 (c = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.03, 2.04, 2.07, 2.23 (12H, 4 x s, $COCH_3$), 4.75 (1H, d, 5'-H), 5.16 (1H, dd, 2'-H), 5.30 (1H, t, 4'-H), 5.58 (1H, t, 3'-H), 6.42 (1H, d, 1'-H); *J*(x-y)/Hz 1'-2' 3.6, 2'-3' 10.3, 3'-4' 9.9, 4'-5' 10.1; δ_C (63 MHz, $CDCl_3$) 20.8 (4 x $COCH_3$), 68.9, 69.1, 69.2, 69.6 (C-1', C-2', C-3', C-4'), 89.1 (C-5'), 155.4 (C-5), 168.8, 169.8, 169.9 (4 x *C*OCH_3), 170.3 (C-2) *m/z*(FAB) M^++1 Found 420.0600. $C_{15}H_{18}NO_{11}S$ requires M^++1 420.0601.

3.10.3 Synthesis of 5-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (205)

3.10.3.1 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol (2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-β-D-glucopyranosylnitromethane) (209)[154]



Lab. Book Ref. KG 337
Molecular Formula $C_{15}H_{21}NO_{11}$
Formula Weight 391

Sodium (2.55 g, 111 mmol, 1.3 eq.) was added portionwise to ice cold dry methanol (90 ml) and left stirring until homogeneous. The resultant solution was added dropwise over a period of 10 min to a solution of D-glucose (15.10 g, 83.8 mmol) in nitromethane (45 ml) and dry

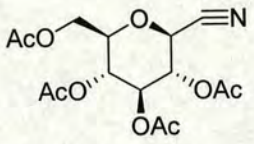
methanol (30 ml), and the mixture left stirring overnight. The resultant solid was filtered off, washed with ice-cold methanol, and sucked dry. This was dissolved quickly in ice-cold water and passed down a column of amberlite IR 120 (plus) resin, for the preparation of the column see section 3.2.4.1. The resin was washed through with water (100 ml) and the combined eluents concentrated *in vacuo* until only ~150 ml remained. The solution was taken onto the next stage without further purification.

The solution produced above was heated at reflux overnight, then activated charcoal (3 g) added and the mixture was refluxed for a further 2 h. The reaction mixture was hot filtered through celite and concentrated *in vacuo* to ~30 ml, then transferred to a liquid-liquid extractor, and extracted over 3 days (water/ethyl acetate). The organic phase was concentrated to give the crude product as orange-brown crystals that were taken onto the next stage without further purification.

Trifluoromethylsulfonic acid (0.1 ml) was added to an ice-cold suspension of the crystals produced above in acetic anhydride (20 ml) under nitrogen. The mixture was allowed to warm to room temperature, and left stirring overnight. Ice-water (*ca.* 100 ml) was added to the reaction mixture, and this was stirred for a further hour, before extracting the product with chloroform. The organic extracts were washed with H_2O (50 ml) and saturated aqueous NaCl (50 ml), then ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resultant dark brown oil was azeotroped with toluene, then dissolved in chloroform (50 ml) and activated charcoal (*ca.* 2 g) added. The mixture was heated to reflux for 30 min and hot-filtered through a celite pad. The solvent was removed *in vacuo*, and the product recrystallised from ethanol to the title compound as a white solid (4.86 g, 15% over three steps); mp 143-144°C (lit.[159] 144-145°C); δ_H (250 MHz, $CDCl_3$) 1.99, 2.01, 2.05, 2.07 (12H, 4 x s, $COCH_3$), 3.74 (1H, m, 6-H), 4.03 (1H, dd, 7a-H), 4.29 (2H, m, 2-H, 7b-H), 4.42 (1H, dd, 1a-H), 4.53 (1H, dd, 1b-H), 4.93 (1H, t, 3-H), 5.07 (1H, t, 5-H), 5.26 (1H, t, 4-H); *J*(x-y)/Hz 1a-1b 13.6, 1a-2 2.7, 1b-2 10.0, 2-3 9.7, 3-4 9.6, 5-6 9.7, 6-7a 2.1, 6-7b nd, 7a-7b 12.5, δ_C (63 MHz, $CDCl_3$) 20.4, 20.5 (4 x $COCH_3$), 61.4 (C-7), 67.7, 69.1, 73.4, 74.2, 75.7 (C-2, C-3, C-4, C-5, C-6), 75.5 (C-1), 169.2, 169.5, 169.9, 170.4 (4 x $COCH_3$); *m/z*(FAB) M^++1 Found 392.1189. $C_{15}H_{22}NO_{11}$ requires M^++1 392.1193.

3.10.3.2 2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-*β*-D-glucopyranosylnitrile (208)[105]

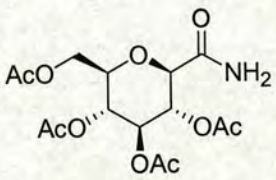
Lab. Book Ref. KG 334
Molecular Formula $C_{15}H_{19}NO_9$
Formula Weight 357



Phosphorous trichloride (0.4 ml, 4.58 mmol, 1.2 eq.) was added to an ice-cold solution of **209** (1.50 g, 3.84 mmol) in pyridine under nitrogen; the reaction mixture was allowed to warm to room temperature and left stirring for 72 h. The resultant dark-brown mixture was quenched with ice-cold aqueous HCl (1M, *ca.* 150 ml) and left stirring for 1 h then extracted with chloroform (3 x 150 ml). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (100 ml), H_2O (50 ml) and saturated aqueous NaCl (50 ml). The organic layers were then dried ($MgSO_4$) and the solvent removed *in vacuo* to give an orange-brown oil. This was dissolved in DCM (*ca.* 100 ml), passed through a silica pad and concentrated *in vacuo* to give the title compound as a white solid (812 mg, 59%); mp 110-111°C (lit.[172] 114-115°C); R_f 0.33 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 2.03, 2.04, 2.11 (12H, 4 x s, $COCH_3$), 3.73 (1H, m, 6-H), 4.20 (2H, ddd, 7a-H, 7b-H), 4.33 (1H, d, 2-H), 5.07-5.22 (2H, m, 3-H, 5-H), 5.32 (1H, t, 4-H); *J*(x-y)/Hz 2-3 10.1, 3-4 9.8, 4-5 9.8, 5-6 9.4, 6-7a 4.8, 6-7b 2.3, 7a-7b 12.7; δ_C (63 MHz, $CDCl_3$) 20.3 (4 x $COCH_3$), 61.3 (7-C), 66.3, 67.1, 68.8, 72.7, 76.7 (C-2. C-3, C-4, C-5, C-6), 114.0 (C-1), 168.6, 169.0, 169.9, 170.4 (4 x $COCH_3$); *m/z*(FAB) M^++1 Found 358.1137. $C_{15}H_{20}NO_9$ requires M^++1 358.1138.

3.10.3.3 *C*-(2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-*β*-D-glucopyranosyl)formamide (210)[143]

Lab. Book Ref. KG 336
Molecular Formula $C_{15}H_{21}NO_{10}$
Formula Weight 375



Titanium tetrachloride (0.05 ml, 0.45 mmol, 0.16 eq.) and water (0.06 ml, 3.3 mmol, 1.2 eq.) were added to an ice-cold solution of nitrile **208** (1.00 g, 2.80 mmol) in glacial acetic acid (5 ml) and stirred at 0°C for ~30 min. The reaction mixture was allowed to warm to room temperature and left stirring for 5 days. Then it was poured into stirred ice-water (50 ml) and the product extracted with chloroform (3 x 50 ml). The organic extracts were combined, washed with saturated $NaHCO_3$ solution (50 ml) and saturated NaCl (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting solid was

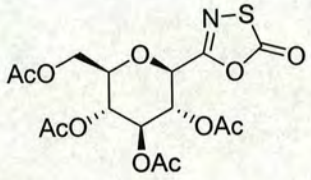
recrystallised from chloroform/Et_2O (1:5) to give the title compound as fine white crystals (478 mg, 46%); mp partially 112-114°C, totally 146-147°C (lit.[105] partially 112-114°C, totally 146-147°C); $[\alpha]_D^{25}$ +103.1 (c = 0.98, $CHCl_3$); R_f 0.05 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 1.81, 1.85, 1.88, 1.93 (12H, 4 x s, $COCH_3$), 3.57-3.59 (1H, m, 6-H), 3.69 (1H, d, 2-H), 4.00 (2H, ddd, 7a-H, 7b-H), 5.10 (1H, t, 3-H), 5.28 (1H, t, 5-H), 5.42 (1H, t, 4-H), 5.49 (1H, broad s, NH) 6.20 (1H, broad s, NH); *J*(x-y)/Hz 2-39.6, 3-4 9.7, 4-5 9.7, 5-6 10.3, 6-7a 2.2, 6-7b 7.0, 7a-7b 13.0; δ_C (63 MHz, $CDCl_3$) 20.2, 20.4, 20.5 (4 x $COCH_3$), 61.8 (C-7), 66.4, 68.1, 73.6, 75.0, 75.9 (C-2, C-3, C-4, C-5, C-6), 169.1, 169.8, 170.4, 170.5 (C-1, 4 x $COCH_3$); *m/z*(FAB) M^++1 Found 376.1243. $C_{15}H_{22}NO_{10}$ requires M^++1 376.1244.

3.10.3.4 5-(2',3',4',6'-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (205)

Lab. Book Ref. KG 373

Molecular Formula $C_{16}H_{19}NO_{11}S$

Formula Weight 433

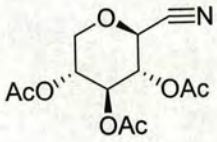


Chlorocarbonylsulfenyl chloride (0.1ml, 1.2 mmol, 4.5 eq.) was added to a solution of **210** (100 mg, 0.27 mmol) in Na-dried toluene (3 ml), and the mixture heated at reflux for 4 h. The reaction mixture was concentrated *in vacuo*, azeotroped with toluene, then passed through a silica pad [cyclohexane:ethyl acetate, 1:1 (50 ml)] and concentrated *in vacuo* to give the title compound as a white solid (88 mg, 75%); mp 112-113°C; $[\alpha]_D^{25}$ +1.8 (c = 1.64, $CHCl_3$); R_f 0.43 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 2.02, 2.03, 2.07, 2.09 (12H, 4 x s, $COCH_3$), 3.70-3.86 (1H, m, 5'-H), 4.06-4.19 (2H, m, 6'a-H, 6b'-H), 4.48 (1H, d, 1'-H), 5.17 (1H, t, 2'-H), 5.30 (1H, t, 4'-H), 5.52 (1H, t, 3'-H); *J*(x-y)/Hz 1'-2' 10.0, 2'-3' 9.6, 3'-4' 9.6, 4'-5' 9.4, 5'-6a' nd, 5'-6b' nd, 6a'-6b' nd; δ_C (63 MHz, $CDCl_3$) 20.3, 20.4 (4 x $COCH_3$), 61.5 (C-6'), 66.3, 67.9, 70.2, 72.8, 73.8 (C-1', C-2', C-3', C-4', C-5'), 156.1 (C-5), 168.9, 169.3, 169.7 (4 x $COCH_3$) 170.0 (C-2); *m/z*(FAB) M^++1 Found 434.0752. $C_{16}H_{20}NO_{11}S$ requires M^++1 434.0757.

3.10.4 Reactions of Oxathiazolones

3.10.4.1 Decomposition of 5-(2',3',4'-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (203)

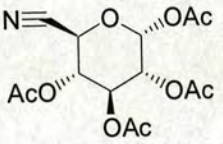
Lab. Book Ref. KG 297
Molecular Formula $C_{12}H_{15}NO_7$
Formula Weight 285



Oxathiazolone **203** (101 mg, 0.28 mmol) was dissolved in *m*-xylene (5 ml) and the solution was heated at reflux, in the absence of a dipolarophile, for 36 h. Once cooled the solvent was removed *in vacuo* and the resulting oil was co-evaporated with toluene to give the nitrile decomposition product **107** as a white solid (80 mg, 100%).

3.10.4.2 Decomposition of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)-1,3,4-oxathiazol-2-one (204)

Lab. Book Ref. KG 335
Molecular Formula $C_{14}H_{17}NO_9$
Formula Weight 343



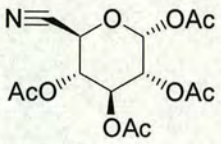
Oxathiazolone **204** (50 mg, 0.14 mmol) was dissolved in mesitylene (5 ml) was heated at reflux under a nitrogen atmosphere for 12 h. The reaction mixture was concentrated *in vacuo* the residual solvent was removed by azeotroping with toluene. The resulting white solid was identified as 1,2,3,4-tetra-*O*-acetyl-α-D-*gluco*-pyranos-5-ylnitrile (**210**) (40 mg, 97%); mp 212-215°C; $[\alpha]_D^{25}$ +83.9 (c = 0.62, $CHCl_3$); R_f 0.65 (petroleum ether:ethyl acetate, 1:1); δ_H (250 MHz, $CDCl_3$) 2.28, 2.30, 2.37, 2.47 (12H, 4 x s, $COCH_3$), 4.98 (1H, d, 5-H), 5.35 (1H, dd, 2-H), 5.54-5.70 (2H, m, 3-H, 4-H), 6.62 (1H, d, 1-H); *J*(x-y)/Hz 1-2 3.7, 2-3 9.5, 3-4 nd, 4-5 10.0; δ_C (63 MHz, $CDCl_3$) 20.2, 20.6 (4 x $COCH_3$), 61.0, 68.1, 68.5, 68.6 (C-1, C-2, C-3, C-4), 88.3 (C-5), 114.0 (C-6), 167.9, 168.6, 169.2, 169.8 (4 x $COCH_3$); *m/z*(FAB) M^++1 Found 344.0979. $C_{14}H_{18}NO_9$ requires M^++1 344.0982; Calc. For $C_{14}H_{17}NO_9$: C, 48.98; H, 4.99; N, 4.08. Found: C, 48.97; H, 5.38; N, 3.68%.

3.10.4.3 1,2,3,4-tetra-*O*-acetyl-α-D-*gluco*-pyranosylnitrile (210)

Lab. Book Ref. KG 374

Molecular Formula $C_{14}H_{17}NO_9$

Formula Weight 34



A solution of amide **207** (220 mg, 0.61 mmol) in thionyl chloride (1.0 ml) was heated to reflux for 72 h, then passed through a silica pad (eluting with 1:1 cyclohexane:ethyl acetate (50 ml)) and concentrated *in vacuo* to give 1,2,3,4-tetra-*O*-acetyl-α-D-*gluco*-pyranosyl nitrile (**210**) as a white solid (155 mg, 74%).[173]

3.10.4.4 Attempted Cycloaddition of 5-(2',3',4'-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (203) with Ethyl Cyanoformate (ECF)

Lab. Book Ref. KG 341

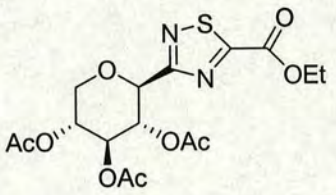
Oxathiazolone **203** (100 mg, 0.28 mmol) and ECF (250 mg, 2.52 mmol, 9eq.) were dissolved in *m*-xylene under nitrogen, the solution was heated at reflux for 72 h. The reaction mixture was cooled and the solvent was removed *in vacuo*, the resulting oil was co-evaporated with toluene to remove the residual ECF to give a white solid (38 mg). The tlc showed only one spot for the starting material but the ^{1}H NMR and mass spectrum indicated it was shown that a mixture of the starting material and the nitrile was present in a 1:1 ratio.

3.10.4.5 Attempted Cycloaddition of 5-(2',3',4'-Tri-*O*-acetyl-β-D-*xylo*-pyranosyl)-1,3,4-oxathiazol-2-one (203) with Dimethyl Acetylenedicarboxylate (DMAD)

Lab. Book Ref. KG 298

Oxathiazolone **203** (100 mg, 0.28 mmol) and DMAD (358 mg, 2.52 mmol, 9eq.) were dissolved in *m*-xylene under nitrogen, the solution was heated at reflux for 48 h. The reaction mixture was cooled and the solvent was removed *in vacuo* the resulting oil was co-evaporated with toluene to remove the residual DMAD to give the nitrile decomposition product as a white solid (79 mg, 100%).

3.10.4.6 Ethyl 3-(2',3',4'-tri-*O*-acetyl-β-D-*xylo*-furanosyl)-1,2,4-thiadiazole-5-carboxylate (212)



Lab. Book Ref. KG 345A

Molecular Formula $C_{16}H_{20}NO_9S$

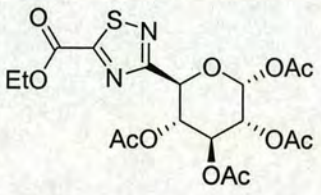
Formula Weight 402

A) Oxathiazolone **203** (100 mg, 0.28 mmol) and ECF (472 mg, 4.76mmol, 17eq.) were dissolved in mesitylene, the solution was irradiated with microwaves for 5 min (225 W, 130°C). The reaction mixture was cooled and the solvent was removed *in vacuo*, the resulting oil was co-evaporated with toluene to remove the residual ECF that yielded a white solid containing a mixture of compounds. The tlc showed several spots and the mass spectrum indicated the presence of the cycloadduct, the starting material and the two decomposition products (nitrile **107** and amide **206**). The reaction mixture was then subjected to preparative tlc to yield the starting material (48 mg, 48%), the nitrile (7 mg, 8%) and the amide (6 mg, 7%), it was not possible to isolate the cycloadduct via this method.

B) Oxathiazolone **203** (100 mg, 0.28 mmol) and ECF (472 mg, 4.76 mmol, 17eq.) were dissolved in mesitylene under nitrogen and irradiated with microwaves for 10 min (225 W, 130°C), in an effort to maximise the yield of the reaction. The reaction mixture was cooled and the solvent was removed *in vacuo* the resulting oil was co-evaporated with toluene to remove the residual ECF that afforded a white solid containing a mixture of compounds. The tlc showed several spots and the mass spectrum indicated the presence of the cycloadduct, and two decomposition products (nitrile **107** and amide **206**). The reaction mixture was then subjected to preparative tlc to yield the nitrile **107** (18 mg, 23%) and the amide **206** (27 mg, 32%), again it was not possible to isolate the cycloadduct by this method.

3.10.4.7 Ethyl 3-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (213): Method 1

This expt. was carried out in collaboration with Mr M. Tackkett

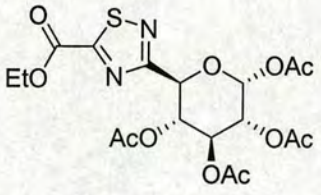


Lab. Book Ref. n/a
Molecular Formula $C_{18}H_{22}N_2O_{11}S$
Formula Weight 474

A solution of oxathiazolone **204** (500 mg, 1.2 mmol) and ECF (2.0 ml, 20.2 mmol, 16.9 eq.) in mesitylene (30 ml) was heated at reflux under a nitrogen atmosphere for 24 h. Mass spectrometry and tlc confirmed no starting material remained, so the reaction mixture was concentrated *in vacuo* and azeotroped with toluene to give a light yellow-brown solid. Purified by column chromatography (silica, 0→100% ethyl acetate in cyclohexane, gradient elution) to give 212 mg of a mixed fraction containing cycloadduct **213** and the corresponding nitrile **210**. Successive preparative tlc (98:2 DCM:methanol) gave the title compound as a white solid (6 mg, 1%); δ_H (250 MHz, $CDCl_3$) 1.46 (3H, t, CH_3CH_2OOC), 1.92, 2.07, 2.08, 2.23 (12H, 4 x s, $COCH_3$), 4.53 (2H, q, CH_3CH_2), 5.29 (1H, dd, 2'-H), 5.37 (1H, d, 5'-H), 5.52 (1H, t, 4'-H), 5.67 (1H, t, 3'-H), 6.49 (1H, d, 1'-H); *J*(x-y)/Hz CH_3CH_2 7.1, 1'-2' 3.8, 2'-3' 10.4, 3'-4' 9.7, 4'-5' 9.8; *m/z*(FAB) M^++1 Found 475.1034. $C_{18}H_{23}N_2O_{11}S$ requires M^++1 475.1023.

3.10.4.8 Ethyl 3-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pyranos-5'-yl)-1,2,4-thiadiazole-5-carboxylate (213): Method 2

This expt. was carried out in collaboration with Mr M. Tackkett



Lab. Book Ref. KG 393
Molecular Formula $C_{18}H_{22}N_2O_{11}S$
Formula Weight 474

Oxathiazolone **204** (105 mg, 0.25 mmol) and ECF (0.42 ml, 4.25 mmol, 17eq.) were dissolved in mesitylene and was irradiated with microwaves for 15 min (225 W, 130°C), in an effort to maximise the yield of the reaction. The reaction mixture was cooled and the solvent was removed *in vacuo*, the resulting oil was co-evaporated with toluene to remove

the residual ECF that left a white solid (47 mg), which contained the starting material and a small quantity of the title compound.

3.10.4.9 Attempted Reaction of 5-(1',2',3',4'-Tetra-*O*-acetyl-α-D-*gluco*-pentopyranos-5'-yl)1,3,4-oxathiazol-2-one (204) and DMAD

Lab. Book Ref. n/a: This expt. was carried out in collaboration with Mr M. Tackkett

A solution of **204** (500 mg, 1.2 mmol) and DMAD (2.2 ml, 17.9 mmol, 15 eq.) in mesitylene (30 ml) was heated at reflux under a nitrogen atmosphere for 24 h. It was indicated by tlc that some starting material remained, and the mass spectrum showed no product peaks. After cooling, large crystals had formed in the reaction mixture; these were removed by filtration and washed with diethyl ether to give oxathiazolone **204** (306 mg, 61%). The filtrate was concentrated *in vacuo*, azeotroped with toluene, and purified by column chromatography (silica, 0→100% ethyl acetate in cyclohexane, gradient elution) to give nitrile **210** (94 mg, 23%), but no cycloadduct could be detected.

3.10.4.10 Attempted Reaction of 5-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (205) and ECF

Lab Book Ref. KG 380

Oxathiazolone **205** (148 mg, 0.34 mmol) and ECF (0.57 ml, 5.78 mmol, 17 eq.) were dissolved in mesitylene under nitrogen and the solution was irradiated with microwaves for 15 min (225 W, 130°C), in an effort to maximise the yield of the reaction. The reaction mixture was cooled and the solvent was removed *in vacuo* the resulting oil was co-evaporated with toluene to remove the residual ECF to give a white solid, which contained nitrile **208** and the starting material (84 mg, 57%).

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Appendix 1: X-ray Crystal Data for 129

Table 1. Crystal data and structure refinement for kg127a.

Contact	Alice Dawson @ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C19 H21 N O8 C19 H21 N O8
Formula weight	391.37
Wavelength	0.71073 A
Temperature	150(2) K
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 9.0722(14) A alpha = 90 deg. b = 5.5871(8) A beta = 92.223(3) deg. c = 18.620(3) A gamma = 90 deg.
Volume	943.1(2) A^3
Number of reflections for cell	2087 (2.03 < theta < 26.24 deg.)
Z	2
Density (calculated)	1.378 Mg/m^3
Absorption coefficient	0.108 mm^-1
F(000)	412
B. DATA COLLECTION	
Crystal description	colourless Plate
Crystal size	0.30 x 0.23 x 0.08 mm
Theta range for data collection	2.19 to 26.44 deg.
Index ranges	-9<=h<=11, -6<=k<=6, -23<=l<=22
Reflections collected	5432
Independent reflections	2125 [R(int) = 0.0354]
Scan type	\w scans
Absorption correction	Multiscan (Tmin= 0.8908, Tmax=1.0)
C. SOLUTION AND REFINEMENT.	
Solution	direct (SHELXS-97 (Sheldrick, 1990))

Refinement type	Full-matrix least-squares on F^2
Program used for refinement	SHELXL-97
Hydrogen atom placement	geom
Hydrogen atom treatment	riding, Me gps riding rotating
Data / restraints / parameters	2125/1/256
Goodness-of-fit on F^2	1.163
Conventional R [F>4sigma(F)]	R1 = 0.0486 [1935 data]
Weighted R (F^2 and all data)	wR2 = 0.1001
Absolute structure parameter	0(10)
Final maximum delta/sigma	0.000
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0356P)^2^+0.1749P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.210 and -0.189 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for kg127a. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(5)	2671(3)	65(6)	7057(2)	23(1)
C(4)	1348(3)	-1417(6)	6817(2)	22(1)
C(3)	450(4)	444(6)	6423(2)	22(1)
C(31)	-854(3)	-48(6)	5942(2)	24(1)
C(32)	-1320(4)	1603(7)	5422(2)	29(1)
C(33)	-2554(4)	1103(8)	4976(2)	38(1)
C(34)	-3301(4)	-1023(8)	5044(2)	40(1)
C(35)	-2841(4)	-2683(8)	5562(2)	42(1)
C(36)	-1615(4)	-2196(7)	6005(2)	33(1)
N(2)	879(3)	2603(6)	6551(1)	26(1)
O(1)	2138(2)	2487(4)	7041(1)	26(1)
C(10)	3327(3)	-567(6)	7804(2)	23(1)
O(101)	2290(2)	-24(5)	8338(1)	28(1)
C(102)	1893(4)	-1865(8)	8773(2)	33(1)
O(103)	2254(3)	-3895(5)	8691(1)	45(1)
C(104)	934(4)	-955(9)	9350(2)	49(1)
C(9)	4754(3)	734(6)	7997(2)	23(1)
O(91)	5353(2)	-620(4)	8604(1)	27(1)
C(92)	6122(4)	505(7)	9141(2)	28(1)
O(93)	6383(3)	2623(5)	9142(1)	36(1)
C(94)	6577(4)	-1241(8)	9713(2)	39(1)
C(8)	5805(3)	698(6)	7387(2)	23(1)
O(81)	6924(2)	2512(4)	7505(1)	27(1)
C(82)	8229(4)	1823(6)	7832(2)	26(1)
O(83)	8540(3)	-234(5)	7942(1)	35(1)

C(84)	9127(4)	3951(7)	8047(2)	33(1)
C(7)	5002(4)	1362(7)	6682(2)	29(1)
O(6)	3774(2)	-205(4)	6549(1)	26(1)

Table 3. Bond lengths [A] and angles [deg] for kg127a.

C(5)-O(6)	1.412(4)
C(5)-O(1)	1.436(4)
C(5)-C(4)	1.511(4)
C(5)-C(10)	1.533(4)
C(4)-C(3)	1.497(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(3)-N(2)	1.287(4)
C(3)-C(31)	1.481(4)
C(31)-C(36)	1.392(5)
C(31)-C(32)	1.392(5)
C(32)-C(33)	1.396(5)
C(32)-H(32)	0.9500
C(33)-C(34)	1.376(6)
C(33)-H(33)	0.9500
C(34)-C(35)	1.390(6)
C(34)-H(34)	0.9500
C(35)-C(36)	1.386(5)
C(35)-H(35)	0.9500
C(36)-H(36)	0.9500
N(2)-O(1)	1.436(3)
C(10)-O(101)	1.428(4)
C(10)-C(9)	1.515(4)
C(10)-H(10)	1.0000
O(101)-C(102)	1.366(5)
C(102)-O(103)	1.192(5)
C(102)-C(104)	1.498(6)
C(104)-H(104A)	0.9800
C(104)-H(104B)	0.9800
C(104)-H(104C)	0.9800
C(9)-O(91)	1.447(4)
C(9)-C(8)	1.512(4)
C(9)-H(9)	1.0000
O(91)-C(92)	1.353(4)
C(92)-O(93)	1.207(5)
C(92)-C(94)	1.490(5)
C(94)-H(94A)	0.9800
C(94)-H(94B)	0.9800
C(94)-H(94C)	0.9800
C(8)-O(81)	1.445(4)
C(8)-C(7)	1.522(4)
C(8)-H(8)	1.0000
O(81)-C(82)	1.366(4)
C(82)-O(83)	1.199(4)
C(2)-C(84)	1.487(5)
C(84)-H(84A)	0.9800
C(84)-H(84B)	0.9800
C(84)-H(84C)	0.9800
C(7)-O(6)	1.431(4)
C(7)-H(71)	0.9900
C(7)-H(72)	0.9900

O(6)-C(5)-O(1)	109.5(3)
O(6)-C(5)-C(4)	108.6(3)
O(1)-C(5)-C(4)	104.3(2)
O(6)-C(5)-C(10)	108.8(2)
O(1)-C(5)-C(10)	110.7(3)
C(4)-C(5)-C(10)	114.7(3)
C(3)-C(4)-C(5)	100.1(3)
C(3)-C(4)-H(4A)	111.8
C(5)-C(4)-H(4A)	111.8
C(3)-C(4)-H(4B)	111.8
C(5)-C(4)-H(4B)	111.8
H(4A)-C(4)-H(4B)	109.5
N(2)-C(3)-C(31)	121.0(3)
N(2)-C(3)-C(4)	113.9(3)
C(31)-C(3)-C(2)	125.1(3)
C(36)-C(31)-C(32)	119.5(3)
C(36)-C(31)-C(3)	119.8(3)
C(32)-C(31)-C(3)	120.8(3)
C(31)-C(32)-C(33)	119.8(4)
C(31)-C(32)-H(32)	120.1
C(33)-C(32)-H(32)	120.1
C(34)-C(33)-C(32)	120.3(4)
C(34)-C(33)-H(33)	119.9
C(32)-C(33)-H(33)	119.9
C(33)-C(34)-C(35)	120.3(4)
C(33)-C(34)-H(34)	119.8
C(35)-C(34)-H(34)	119.8
C(36)-C(35)-C(34)	119.6(4)
C(36)-C(35)-H(35)	120.2
C(34)-C(35)-H(35)	120.2
C(35)-C(36)-C(31)	120.5(3)
C(35)-C(36)-H(36)	119.7
C(31)-C(36)-H(36)	119.7
C(3)-N(2)-O(1)	107.6(3)
N(2)-O(1)-C(5)	108.3(2)
O(101)-C(10)-C(9)	108.2(3)
O(101)-C(10)-C(5)	109.8(2)
C(9)-C(10)-C(5)	113.8(3)
O(101)-C(10)-H(10)	108.3
C(9)-C(10)-H(10)	108.3
C(5)-C(10)-H(102)	108.3
C(102)-O(101)-C(10)	116.7(3)
O(103)-C(102)-O(101)	124.1(4)
O(103)-C(102)-C(104)	125.8(4)
O(101)-C(102)-C(104)	110.1(4)
C(102)-C(104)-H(104A)	109.5
C(102)-C(104)-H(104B)	109.5
H(104A)-C(104)-H(104B)	109.5
C(102)-C(104)-H(104C)	109.5
H(104A)-C(104)-H(104C)	109.5
H(104B)-C(104)-H(104C)	109.5
O(91)-C(9)-C(8)	110.6(2)
O(91)-C(9)-C(10)	103.1(3)
C(8)-C(9)-C(10)	111.9(3)
O(91)-C(9)-H(9)	110.4
C(8)-C(9)-H(9)	110.4
C(10)-C(9)-H(9)	110.4
C(92)-O(91)-C(9)	120.2(3)
O(93)-C(92)-O(91)	123.5(3)
O(93)-C(92)-C(94)	126.3(3)
O(91)-C(92)-C(94)	110.2(3)

C(2)-C(94)-H(94A)	109.5
C(92)-C(94)-H(94B)	109.5
H(94A)-C(94)-H(94B)	109.5
C(92)-C(94)-H(94C)	109.5
H(94A)-C(94)-H(94C)	109.5
H(94B)-C(94)-H(94C)	109.5
O(81)-C(8)-C(9)	109.6(3)
O(81)-C(8)-C(7)	105.7(2)
C(9)-C(8)-C(7)	110.5(3)
O(81)-C(8)-H(8)	110.3
C(9)-C(8)-H(8)	110.3
C(7)-C(8)-H(8)	110.3
C(82)-O(81)-C(8)	117.5(3)
O(83)-C(82)-O(81)	122.8(3)
O(83)-C(82)-C(84)	126.7(3)
O(81)-C(82)-C(84)	110.5(3)
C(82)-C(84)-H(84A)	109.5
C(82)-C(84)-H(84B)	109.5
H(84A)-C(84)-H(84B)	109.5
C(82)-C(84)-H(84C)	109.5
H(84A)-C(84)-H(84C)	109.5
H(84B)-C(84)-H(84C)	109.5
O(6)-C(7)-C(8)	110.1(3)
O(6)-C(7)-H(71)	109.6
C(8)-C(7)-H(71)	109.6
O(6)-C(7)-H(72)	109.6
C(8)-C(7)-H(72)	109.6
H(71)-C(7)-H(72)	108.2
C(5)-O(6)-C(7)	112.7(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for kg127a. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(5)	22(2)	22(2)	25(2)	-4(1)	3(1)	-2(1)
C(4)	22(2)	18(2)	25(2)	0(1)	-4(1)	-1(1)
C(3)	23(2)	20(2)	24(2)	-1(1)	-1(1)	1(1)
C(31)	22(2)	28(2)	22(2)	-5(2)	-1(1)	5(2)
C(32)	29(2)	30(2)	27(2)	4(2)	3(1)	5(2)
C(33)	36(2)	53(3)	23(2)	4(2)	-2(2)	17(2)
C(34)	36(2)	48(3)	34(2)	-15(2)	-10(2)	7(2)
C(35)	35(2)	33(2)	58(2)	-11(2)	-14(2)	3(2)
C(36)	29(2)	30(2)	39(2)	1(2)	-8(2)	2(2)
N(2)	24(1)	31(2)	25(1)	2(1)	-4(1)	1(1)
O(1)	25(1)	22(1)	29(1)	-2(1)	-5(1)	0(1)
C(10)	20(2)	23(2)	25(2)	1(1)	-1(1)	-1(1)
O(101)	22(1)	33(1)	29(1)	4(1)	3(1)	-3(1)
C(102)	25(2)	48(3)	25(2)	4(2)	-9(1)	-15(2)
O(103)	59(2)	38(2)	38(2)	10(1)	1(1)	-19(2)
C(104)	36(2)	79(4)	33(2)	-1(2)	4(2)	-9(2)

C(9)	23(2)	21(2)	24(2)	4(1)	-4(1)	1(1)
O(91)	27(1)	30(1)	24(1)	2(1)	-2(1)	-3(1)
C(92)	20(2)	42(2)	22(2)	-6(2)	2(1)	-3(2)
O(93)	39(2)	35(2)	34(1)	-6(1)	-3(1)	-8(1)
C(94)	35(2)	51(3)	30(2)	4(2)	-6(2)	-7(2)
C(8)	18(2)	23(2)	27(2)	0(1)	1(1)	-2(1)
O(81)	23(1)	25(1)	34(1)	3(1)	-3(1)	-2(1)
C(82)	21(2)	29(2)	27(2)	-1(2)	5(1)	-2(2)
O(83)	26(1)	28(2)	50(2)	1(1)	-5(1)	1(1)
C(84)	24(2)	34(2)	40(2)	-1(2)	1(2)	-3(2)
C(7)	26(2)	34(2)	28(2)	2(2)	1(1)	-4(2)
O(6)	22(1)	33(1)	23(1)	-6(1)	0(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for kg127a.

	x	y	z	U(eq)
H(4A)	1626	-2743	6497	26
H(4B)	826	-2071	7231	26
H(32)	-800	3065	5370	34
H(33)	-2881	2237	4624	45
H(34)	-4134	-1359	4736	47
H(35)	-3364	-4142	5612	51
H(36)	-1291	-3337	6355	39
H(10)	3526	-2327	7818	27
H(104A)	1431	-1208	9821	74
H(104B)	-6	-1821	9330	74
H(104C)	751	758	9278	74
H(9)	4546	2419	8144	27
H(94A)	5813	-1329	10070	59
H(94B)	7509	-720	9947	59
H(94C)	6709	-2823	9497	59
H(8)	6271	-916	7348	27
H(84A)	10173	3510	8077	49
H(84B)	8827	4525	8516	49
H(84C)	8973	5220	7688	49
H(71)	4650	3037	6706	35
H(72)	5688	1241	6283	35

Appendix 2: X-ray Crystal Data for 133

Table 1. Crystal data and structure refinement for kmg204.

Contact	Andy Parkin, a.parkin@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C42 H41 N O6 C42 H41 N O6
Formula weight	655.76
Wavelength	0.71073 A
Temperature	150(2) K
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 23.355(4) A alpha = 90 deg. b = 5.8198(11) A beta = 112.270(2) deg. c = 27.228(5) A gamma = 90 deg.
Volume	3424.8(11) A^3
Number of reflections for cell	4966 (2.4 < theta < 28.9 deg.)
Z	4
Density (calculated)	1.272 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	1392
B. DATA COLLECTION	
Crystal description	Colourless lath
Crystal size	1.42 x 0.39 x 0.13 mm
Theta range for data collection	1.62 to 23.50 deg.
Index ranges	-26<=h<=26, -6<=k<=6, -30<=l<=30
Reflections collected	11049
Independent reflections	5062 [R(int) = 0.0344]
Scan type	phi scans
Absorption correction	Semi-empirical from equivalents (Tmin= 0.612, Tmax=1.000)
C. SOLUTION AND REFINEMENT.	

Solution	direct (sir92)
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	SHELXL-97
Hydrogen atom placement	geometric
Hydrogen atom treatment	riding
Data / restraints / parameters	5062/1/443
Goodness-of-fit on F^2	1.074
Conventional R [F>4sigma(F)]	R1 = 0.0543 [4467 data]
Weighted R (F^2 and all data)	wR2 = 0.1251
Absolute structure parameter	0.0(8)

Absolute structure determined from precursor of known hand.

Extinction coefficient	0
Final maximum delta/sigma	0.000

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.0541P)^2^+1.3703P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.385 and -0.361 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for kmg204. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-9689(1)	-4672(4)	-3255(1)	34(1)
N(2)	-10341(1)	-4808(5)	-3554(1)	31(1)
C(3)	-10580(1)	-2834(5)	-3544(1)	26(1)
C(31)	-11243(1)	-2417(6)	-3820(1)	29(1)
C(32)	-11629(1)	-4097(6)	-4143(1)	36(1)
C(33)	-12257(2)	-3697(7)	-4398(1)	39(1)
C(34)	-12505(1)	-1640(7)	-4327(1)	41(1)
C(35)	-12125(1)	28(7)	-4009(1)	39(1)
C(36)	-11504(1)	-368(6)	-3755(1)	34(1)
C(4)	-10116(1)	-1068(6)	-3239(1)	34(1)
C(5)	-9556(1)	-2538(6)	-2962(1)	31(1)
C(10)	-8938(1)	-1646(6)	-2941(1)	31(1)
O(101)	-8970(1)	-1301(4)	-3468(1)	35(1)
C(102)	-8828(2)	997(6)	-3570(1)	40(1)
C(103)	-8932(2)	1233(6)	-4148(1)	37(1)
C(104)	-9166(2)	3253(7)	-4414(1)	46(1)
C(105)	-9267(2)	3507(8)	-4946(2)	51(1)
C(106)	-9136(2)	1726(8)	-5212(2)	53(1)
C(107)	-8892(2)	-290(8)	-4954(2)	57(1)

C(108)	-8788(2)	-554(7)	-4420(1)	45(1)
C(9)	-8416(1)	-3288(6)	-2645(1)	40(1)
O(91)	-7834(1)	-2335(5)	-2577(1)	46(1)
C(92)	-7589(2)	-2843(11)	-2972(2)	84(2)
C(93)	-6904(1)	-2969(7)	-2716(1)	40(1)
C(94)	-6528(2)	-1141(7)	-2768(1)	57(1)
C(95)	-5876(2)	-1350(8)	-2512(1)	56(1)
C(96)	-5645(2)	-3282(9)	-2225(2)	59(1)
C(97)	-6008(2)	-4933(8)	-2180(2)	62(1)
C(98)	-6614(2)	-4813(7)	-2420(1)	49(1)
C(8)	-8422(2)	-3781(6)	-2104(1)	42(1)
O(81)	-7987(1)	-5582(4)	-1868(1)	66(1)
C(82)	-7515(2)	-4995(8)	-1373(1)	51(1)
C(83)	-6975(2)	-6582(6)	-1259(1)	39(1)
C(84)	-6418(2)	-5998(7)	-860(1)	51(1)
C(85)	-5904(2)	-7335(8)	-751(2)	60(1)
C(86)	-5931(2)	-9320(8)	-1031(2)	55(1)
C(87)	-6478(2)	-9959(8)	-1428(1)	52(1)
C(88)	-7000(2)	-8601(7)	-1538(1)	46(1)
C(7)	-9057(2)	-4575(7)	-2142(1)	48(1)
C(71)	-9100(2)	-4841(11)	-1605(2)	93(2)
O(72)	-8878(2)	-2887(10)	-1294(1)	119(2)
C(73)	-9268(2)	-1837(9)	-1145(3)	124(3)
C(74)	-8994(2)	136(9)	-755(2)	68(1)
C(75)	-8371(2)	688(8)	-575(2)	67(1)
C(76)	-8131(2)	2501(9)	-236(2)	71(1)
C(77)	-8498(2)	3808(11)	-61(2)	85(2)
C(78)	-9127(2)	3249(13)	-241(2)	93(2)
C(79)	-9362(2)	1460(11)	-582(2)	80(2)
O(6)	-9523(1)	-2933(4)	-2439(1)	39(1)

Table 3. Bond lengths [A] and angles [deg] for kmg204.

O(1)-N(2)	1.431(3)
O(1)-C(5)	1.444(4)
N(2)-C(3)	1.281(4)
C(3)-C(31)	1.464(4)
C(3)-C(4)	1.495(4)
C(31)-C(36)	1.380(5)
C(31)-C(32)	1.393(4)
C(32)-C(33)	1.384(4)
C(33)-C(34)	1.375(5)
C(34)-C(35)	1.378(5)
C(35)-C(36)	1.369(4)
C(4)-C(5)	1.506(4)
C(5)-O(6)	1.416(4)
C(5)-C(10)	1.514(4)
C(10)-O(101)	1.421(4)
C(10)-C(9)	1.517(5)
O(101)-C(102)	1.431(4)
C(102)-C(103)	1.504(4)
C(103)-C(104)	1.380(5)
C(103)-C(108)	1.390(5)
C(104)-C(105)	1.386(5)
C(105)-C(106)	1.364(6)
C(106)-C(107)	1.375(6)
C(107)-C(10	1.389(5)
C(9)-O(91)	1.414(4)

C(9)-C(8)	1.507(5)
O(91)-C(92)	1.428(4)
C(92)-C(93)	1.485(5)
C(93)-C(98)	1.359(5)
C(93)-C(94)	1.422(5)
C(94)-C(95)	1.419(6)
C(95)-C(96)	1.360(6)
C(96)-C(97)	1.316(6)
C(97)-C(98)	1.317(5)
C(8)-O(81)	1.431(4)
C(8)-C(7)	1.519(5)
O(81)-C(82)	1.422(4)
C(82)-C(83)	1.499(5)
C(83)-C(84)	1.385(5)
C(83)-C(88)	1.388(5)
C(84)-C(85)	1.365(5)
C(85)-C(86)	1.373(6)
C(86)-C(87)	1.376(5)
C(87)-C(88)	1.387(5)
C(7)-O(6)	1.445(4)
C(7)-C(71)	1.511(5)
C(71)-O(72)	1.395(7)
O(72)-C(73)	1.281(7)
C(73)-C(74)	1.530(8)
C(74)-C(79)	1.366(7)
C(74)-C(75)	1.385(6)
C(75)-C(76)	1.374(6)
C(76)-C(77)	1.361(7)
C(77)-C(78)	1.398(7)
C(78)-C(79)	1.364(8)

N(2)-O(1)-C(5)	108.8(2)
C(3)-N(2)-O(1)	108.4(2)
N(2)-C(3)-C(31)	121.5(3)
N(2)-C(3)-C(4)	113.5(3)
C(31)-C(3)-C(4)	125.0(3)
C(36)-C(31)-C(32)	118.5(3)
C(36)-C(31)-C(3)	120.6(3)
C(32)-C(31)-C(3)	120.8(3)
C(33)-C(32)-C(31)	120.5(3)
C(34)-C(33)-C(32)	119.9(3)
C(33)-C(34)-C(35)	119.8(3)
C(36)-C(35)-C(34)	120.4(3)
C(35)-C(36)-C(31)	121.0(3)
C(3)-C(4)-C(5)	101.3(3)
O(6)-C(5)-O(1)	109.5(2)
O(6)-C(5)-C(4)	107.4(2)
O(1)-C(5)-C(4)	104.3(2)
O(6)-C(5)-C(10)	109.3(2)
O(1)-C(5)-C(10)	108.6(2)
C(4)-C(5)-C(10)	117.4(3)
O(101)-C(10)-C(5)	108.9(2)
O(101)-C(10)-C(9)	110.5(2)
C(5)-C(10)-C(9)	111.4(3)
C(10)-O(101)-C(102)	113.6(2)
O(101)-C(102)-C(103)	109.3(3)
C(104)-C(103)-C(108)	119.0(3)
C(104)-C(103)-C(102)	120.1(3)
C(108)-C(103)-C(102)	120.9(3)
C(103)-C(104)-C(105)	121.1(4)
C(106)-C(105)-C(104)	119.3(4)

C(105)-C(106)-C(107)	120.7(4)
C(106)-C(107)-C(108)	120.2(4)
C(107)-C(108)-C(103)	119.6(4)
O(91)-C(9)-C(8)	108.1(3)
O(91)-C(9)-C(10)	111.1(3)
C(8)-C(9)-C(10)	109.7(3)
C(9)-O(91)-C(92)	117.4(3)
O(91)-C(92)-C(93)	109.0(3)
C(98)-C(93)-C(94)	117.5(3)
C(98)-C(93)-C(92)	121.6(4)
C(94)-C(93)-C(92)	120.9(4)
C(95)-C(94)-C(93)	118.4(4)
C(96)-C(95)-C(94)	118.1(4)
C(97)-C(96)-C(95)	121.9(4)
C(96)-C(97)-C(98)	121.6(4)
C(97)-C(98)-C(93)	122.5(4)
O(81)-C(8)-C(9)	108.0(3)
O(81)-C(8)-C(7)	108.5(3)
C(9)-C(8)-C(7)	111.1(3)
C(82)-O(81)-C(8)	114.3(3)
O(81)-C(82)-C(83)	109.7(3)
C(84)-C(83)-C(88)	118.0(4)
C(84)-C(83)-C(82)	118.5(3)
C(88)-C(83)-C(82)	123.5(3)
C(85)-C(84)-C(83)	121.1(4)
C(84)-C(85)-C(86)	120.5(4)
C(85)-C(86)-C(87)	119.8(4)
C(86)-C(87)-C(88)	119.6(4)
C(87)-C(88)-C(83)	120.9(3)
O(6)-C(7)-C(71)	107.3(4)
O(6)-C(7)-C(8)	110.3(3)
C(71)-C(7)-C(8)	112.7(3)
O(72)-C(71)-C(7)	111.0(4)
C(73)-O(72)-C(71)	115.9(4)
O(72)-C(73)-C(74)	114.6(4)
C(79)-C(74)-C(75)	117.4(5)
C(79)-C(74)-C(73)	120.7(5)
C(75)-C(74)-C(73)	121.8(5)
C(76)-C(75)-C(74)	121.5(5)
C(77)-C(76)-C(75)	120.9(5)
C(76)-C(77)-C(78)	117.7(5)
C(79)-C(78)-C(77)	121.0(6)
C(78)-C(79)-C(74)	121.4(5)
C(5)-O(6)-C(7)	114.3(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for kmg204. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	29(1)	32(1)	35(1)	-6(1)	6(1)	3(1)

N(2)	24(1)	37(2)	27(1)	-3(1)	2(1)	-2(1)
C(3)	30(2)	30(2)	17(2)	-2(1)	9(1)	1(1)
C(31)	27(2)	40(2)	18(2)	0(2)	7(1)	-1(2)
C(32)	34(2)	41(2)	31(2)	-1(2)	8(1)	-1(2)
C(33)	33(2)	46(2)	36(2)	-6(2)	9(2)	-3(2)
C(34)	25(2)	60(2)	34(2)	4(2)	7(1)	6(2)
C(35)	32(2)	43(2)	36(2)	-1(2)	6(2)	9(2)
C(36)	33(2)	37(2)	27(2)	-5(2)	8(1)	0(2)
C(4)	29(2)	35(2)	36(2)	-10(2)	10(1)	-3(2)
C(5)	33(2)	33(2)	24(2)	-6(2)	9(1)	1(2)
C(10)	33(2)	36(2)	24(2)	-7(2)	10(1)	-2(2)
O(101)	43(1)	36(1)	27(1)	-7(1)	15(1)	-6(1)
C(102)	48(2)	36(2)	39(2)	-9(2)	21(2)	-12(2)
C(103)	36(2)	44(2)	33(2)	-2(2)	17(2)	-10(2)
C(104)	39(2)	48(2)	52(2)	-2(2)	16(2)	-6(2)
C(105)	37(2)	65(3)	48(2)	13(2)	12(2)	-5(2)
C(106)	48(2)	76(3)	35(2)	2(2)	13(2)	-28(2)
C(107)	77(3)	61(3)	43(2)	-16(2)	35(2)	-25(2)
C(108)	58(2)	45(2)	34(2)	-10(2)	20(2)	-11(2)
C(9)	31(2)	45(2)	36(2)	-12(2)	4(2)	1(2)
O(91)	26(1)	72(2)	38(1)	-23(1)	8(1)	2(1)
C(92)	36(2)	146(5)	63(3)	-42(3)	14(2)	6(3)
C(93)	29(2)	61(3)	29(2)	-16(2)	9(1)	5(2)
C(94)	102(3)	44(3)	24(2)	-2(2)	23(2)	19(2)
C(95)	69(3)	69(3)	42(2)	-21(2)	34(2)	-40(3)
C(96)	41(2)	85(4)	48(2)	-10(3)	14(2)	10(2)
C(97)	67(3)	58(3)	54(3)	-5(2)	15(2)	6(3)
C(98)	61(3)	51(2)	40(2)	-8(2)	25(2)	-12(2)
C(8)	38(2)	38(2)	36(2)	1(2)	-2(2)	-1(2)
O(81)	60(2)	41(2)	54(2)	1(1)	-30(1)	1(1)
C(82)	45(2)	56(3)	35(2)	-2(2)	-3(2)	0(2)
C(83)	42(2)	39(2)	29(2)	6(2)	3(2)	-4(2)
C(84)	49(2)	48(3)	45(2)	1(2)	4(2)	-2(2)
C(85)	43(2)	55(3)	60(3)	2(2)	-3(2)	-2(2)
C(86)	52(2)	58(3)	58(3)	8(2)	25(2)	7(2)
C(87)	77(3)	47(2)	39(2)	4(2)	28(2)	7(2)
C(88)	57(2)	45(2)	26(2)	2(2)	4(2)	-10(2)
C(7)	47(2)	52(2)	30(2)	7(2)	-2(2)	-14(2)
C(71)	87(3)	136(5)	37(2)	13(3)	3(2)	-74(4)
O(72)	105(3)	219(5)	42(2)	-49(3)	37(2)	-112(3)
C(73)	37(3)	40(3)	231(8)	28(4)	-21(4)	7(2)
C(74)	41(2)	73(3)	76(3)	36(3)	6(2)	8(2)
C(75)	54(3)	62(3)	70(3)	16(3)	8(2)	4(2)
C(76)	62(3)	83(4)	52(3)	9(3)	6(2)	-13(3)
C(77)	93(4)	112(5)	41(3)	4(3)	14(3)	4(4)
C(78)	79(4)	150(6)	48(3)	27(4)	20(3)	19(4)
C(79)	60(3)	121(5)	48(3)	46(3)	8(2)	-4(3)
O(6)	39(1)	52(2)	26(1)	-5(1)	13(1)	-9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for kmg204.

	x	y	z	U(eq)
H(32)	-11459	-5527	-4189	44
H(33)	-12516	-4843	-4621	47

H(34)	-12937	-1370	-4496	49
H(35)	-12294	1462	-3965	47
H(36)	-11248	784	-3530	40
H(4A)	-10250	-253	-2982	41
H(4B)	-10039	66	-3478	41
H(10)	-8854	-135	-2752	37
H(102A)	-8391	1354	-3349	48
H(102B)	-9095	2095	-3478	48
H(104)	-9259	4489	-4229	56
H(105)	-9426	4909	-5124	61
H(106)	-9214	1878	-5579	64
H(107)	-8795	-1506	-5141	68
H(108)	-8619	-1946	-4241	54
H(9)	-8475	-4757	-2849	48
H(92A)	-7711	-1628	-3247	100
H(92B)	-7756	-4326	-3145	100
H(94)	-6708	189	-2970	68
H(95)	-5609	-173	-2541	68
H(96)	-5210	-3444	-2050	71
H(97)	-5828	-6244	-1971	74
H(98)	-6857	-6063	-2385	59
H(8)	-8299	-2370	-1878	51
H(82A)	-7678	-5118	-1087	61
H(82B)	-7382	-3388	-1384	61
H(84)	-6393	-4644	-658	61
H(85)	-5525	-6888	-479	72
H(86)	-5572	-10251	-950	66
H(87)	-6497	-11321	-1627	63
H(88)	-7379	-9059	-1807	55
H(7)	-9151	-6088	-2330	57
H(71A)	-9536	-5107	-1652	111
H(71B)	-8855	-6195	-1422	111
H(73A)	-9454	-2964	-978	148
H(73B)	-9604	-1220	-1463	148
H(75)	-8104	-208	-688	80
H(76)	-7702	2846	-122	85
H(77)	-8334	5057	175	102
H(78)	-9394	4128	-125	112
H(79)	-9792	1128	-701	96

Appendix 3: X-ray Crystal Data for 204

Table 1. Crystal data and structure refinement for mt025a.

Contact	Alice Dawson, alice.dawson@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C15 H17 N1 O11 S1 C15 H17 N1 O11 S1
Formula weight	419.37
Wavelength	0.71073 A
Temperature	150 K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.8149(7) A alpha = 90 deg. b = 12.787(1) A beta = 90 deg. c = 16.4257(13) A gamma = 90 deg.
Volume	1851.4(3) A^3
Number of reflections for cell	5430 (3 < theta < 28 deg.)
Z	4
Density (calculated)	1.504 Mg/m^3
Absorption coefficient	0.236 mm^-1
F(000)	872.000
B. DATA COLLECTION	
Crystal description	colourless block
Crystal size	0.14 x 0.23 x 0.24 mm
Instrument	Bruker SMART
Theta range for data collection	2.018 to 28.782 deg.
Index ranges	-11<=h<=11, -17<=k<=17, -21<=l<=21
Reflections collected	16665
Independent reflections	4525 [R(int) = 0.03]
Scan type	\f & \w scans (phi and omega scans)
Absorption correction	Semi-empirical from equivalents (Tmin= 0.859225, Tmax=1.0)

C. SOLUTION AND REFINEMENT.

Solution	direct (Shelxs)
Refinement type	Full-matrix least-squares on F squared
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	noref
Data	4524
Parameters	254
Goodness-of-fit on F^2	0.9226
R	0.0474
Rw	0.1003
Absolute structure parameter	-0.08(9)
Final maximum delta/sigma	0.000187
Weighting scheme	Auto-statistical
Largest diff. peak and hole	0.63 and -0.53 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for publish. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(6')	6701(2)	4382(1)	3588(1)	22
C(1')	7945(3)	4749(2)	4045(1)	21
O(11')	7579(2)	5666(1)	4487(1)	23
C(12')	6732(3)	5527(2)	5179(2)	29
C(13')	6525(4)	6543(3)	5601(2)	45
O(13')	6265(2)	4693(2)	5385(1)	37
C(2')	9240(3)	5025(2)	3471(2)	19
O(21')	10486(2)	5473(1)	3901(1)	24
C(22')	11447(3)	4785(2)	4259(2)	28
C(23')	12710(3)	5350(3)	4673(2)	41
O(23')	11276(2)	3861(2)	4233(1)	35
C(3')	8733(2)	5843(2)	2857(1)	18
O(31')	9894(2)	5944(1)	2250(1)	20
C(32')	10569(3)	6894(2)	2163(2)	21
C(33')	11592(3)	6879(2)	1437(2)	34
O(33')	10348(2)	7619(1)	2601(1)	30
C(4')	7300(3)	5491(2)	2423(1)	18
O(41')	6773(2)	6392(1)	1979(1)	20
C(42')	5953(3)	6230(2)	1286(1)	19
C(43')	5686(3)	7240(2)	858(2)	26
O(43')	5537(2)	5384(1)	1070(1)	25
C(5')	6094(3)	5137(2)	3035(1)	19
C(5)	4806(3)	4596(2)	2619(1)	20
O(1)	5191(2)	3695(1)	2223(1)	24
C(2)	3963(3)	3313(2)	1791(2)	27
O(21)	4050(3)	2582(1)	1347(1)	38
S(3)	2404(1)	4104(1)	2033(1)	32
N(4)	3454(2)	4921(2)	2612(1)	24

Table 3. Bond lengths [A] and angles [deg] for publish.

O(6')-C(1')	1.409(3)
O(6')-C(5')	1.429(3)
C(1')-O(11')	1.417(3)
C(1')-C(2)	1.522(3)
C(1')-H(11')	1.002
O(11')-C(12')	1.372(3)
C(12')-C(13')	1.483(4)
C(12')-O(13')	1.192(3)
C(13')-H(131')	1.000
C(13')-H(132')	0.999
C(13')-H(133')	1.004
C(2')-O(21')	1.426(3)
C(2')-C(3')	1.521(3)
C(2')-H(21')	1.001
O(21')-C(22')	1.355(3)
C(22')-C(23')	1.491(4)
C(22')-O(23')	1.193(3)
C(23')-H(231')	1.001
C(23')-H(232')	0.999
C(23')-H(233')	1.002
C(3')-O(31')	1.435(3)
C(3')-C(4')	1.519(3)
C(3')-H(31')	0.999
O(31')-C(32')	1.359(3)
C(32')-C(33')	1.496(4)
C(32')-O(33')	1.190(3)
C(33')-H(331')	0.999
C(33')-H(332')	1.001
C(33')-H(333')	1.004
C(4')-O(41')	1.441(3)
C(4')-C(5')	1.532(3)
C(4')-H(41')	1.000
O(41')-C(42')	1.364(3)
C(42')-C(43')	1.488(3)
C(42')-O(43')	1.196(3)
C(43')-H(431')	1.000
C(43')-H(432')	0.999
C(43')-H(433')	1.002
C(5')-C(5)	1.495(3)
C(5')-H(51')	1.000
C(5)-O(1)	1.366(3)
C(5)-N(4)	1.262(3)
O(1)-C(2)	1.383(3)
C(2)-O(21)	1.188(3)
C(2)-S(3)	1.753(3)
S(3)-N(4)	1.689(2)

C(1')-O(6')-C(5')	113.9(25)
O(6')-C(1')-O(11')	111.8(18)
O(6')-C(1')-C(2')	109.3(3)
O(11')-C(1')-C(2')	107.3(33)
O(6')-C(1')-H(11')	106.997
O(11')-C(1')-H(11')	109.396
C(2')-C(1')-H(11')	112.133
C(1')-O(11')-C(12')	116.2(27)
O(11')-C(12')-C(13')	109.9(42)
O(11')-C(12')-O(13')	122.6(44)
C(13')-C(12')-O(13')	127.51(18)

C(12')-C(13')-H(131')	109.763
C(12')-C(13')-H(132')	109.614
H(131')-C(13')-H(132')	109.551
C(12')-C(13')-H(133')	109.478
H(131')-C(13')-H(133')	109.170
H(132')-C(13')-H(133')	109.249
C(1')-C(2')-O(21')	111.3(5)
C(1')-C(2')-C(3')	110.5(14)
O(21')-C(2')-C(3')	106.1(33)
C(1')-C(2')-H(21')	106.378
O(21')-C(2')-H(21')	110.718
C(3')-C(2')-H(21')	111.866
C(2')-O(21')-C(22')	115.8(28)
O(21')-C(22')-C(23')	110.6(46)
O(21')-C(22')-O(23')	123.2(18)
C(23')-C(22')-O(23')	126.2(28)
C(22')-C(23')-H(231')	109.514
C(22')-C(23')-H(232')	109.614
H(231')-C(23')-H(232')	109.497
C(22')-C(23')-H(233')	109.579
H(231')-C(23')-H(233')	109.209
H(232')-C(23')-H(233')	109.413
C(2')-C(3')-O(31')	108.2(18)
C(2')-C(3')-C(4')	110.6(30)
O(31')-C(3')-C(4')	107.1(6)
C(2')-C(3')-H(31')	108.819
O(31')-C(3')-H(31')	112.141
C(4')-C(3')-H(31')	109.947
C(3')-O(31')-C(32')	117.7(21)
O(31')-C(32')-C(33')	109.6(30)
O(31')-C(32')-O(33')	124.1(7)
C(33')-C(32')-O(33')	126.2(38)
C(32')-C(33')-H(331')	109.785
C(32')-C(33')-H(332')	109.647
H(331')-C(33')-H(332')	109.515
C(32')-C(33')-H(333')	109.531
H(331')-C(33')-H(333')	109.247
H(332')-C(33')-H(333')	109.098
C(3')-C(4')-O(41')	105.6(31)
C(3')-C(4')-C(5')	110.854
O(41')-C(4')-C(5')	110.2(15)
C(3')-C(4')-H(41')	111.345
O(41')-C(4')-H(41')	111.865
C(5')-C(4')-H(41')	107.055
C(4')-O(41')-C(42')	118.1(26)
O(41')-C(42')-C(43')	110.2(35)
O(41')-C(42')-O(43')	123.2(35)
C(43')-C(42')-O(43')	126.61(6)
C(42')-C(43')-H(431')	109.586
C(42')-C(43')-H(432')	109.595
H(431')-C(43')-H(432')	109.575
C(42')-C(43')-H(433')	109.309
H(431')-C(43')-H(433')	109.353
H(432')-C(43')-H(433')	109.408
O(6')-C(5')-C(4')	111.0(11)
O(6')-C(5')-C(5)	105.2(32)
C(4')-C(5')-C(5)	111.3(5)
O(6')-C(5')-H(51')	111.631
C(4')-C(5')-H(51')	105.980
C(5)-C(5')-H(51')	111.848
C(5')-C(5)-O(1)	114.7(13)

C(5')-C(5)-N(4)	124.7(37)
O(1)-C(5)-N(4)	120.6(23)
C(5)-O(1)-C(2)	110.3(12)
O(1)-C(2)-O(21)	122.8(21)
O(1)-C(2)-S(3)	107.1(29)
O(21)-C(2)-S(3)	130.1(8)
C(2)-S(3)-N(4)	93.165(12)
C(5)-N(4)-S(3)	108.6(26)

Symmetry transformations used to generate equivalent atoms:

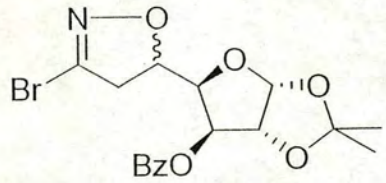
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for publish.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(6')	24(1)	20(1)	22(1)	4(1)	-2(1)	-3(1)
C(1')	22(1)	22(1)	19(1)	3(1)	-1(1)	1(1)
O(11')	24(1)	28(1)	16(1)	1(1)	1(1)	2(1)
C(12')	21(1)	49(2)	16(1)	5(1)	-3(1)	7(1)
C(13')	56(2)	56(2)	22(1)	-6(1)	8(1)	15(2)
O(13')	28(1)	54(1)	27(1)	13(1)	4(1)	-4(1)
C(2')	18(1)	18(1)	22(1)	-1(1)	-2(1)	1(1)
O(21')	21(1)	28(1)	22(1)	2(1)	-3(1)	0(1)
C(22')	21(1)	42(2)	20(1)	5(1)	4(1)	8(1)
C(23')	29(2)	64(2)	31(1)	2(2)	-10(1)	4(2)
O(23')	33(1)	36(1)	36(1)	10(1)	-1(1)	12(1)
C(3')	17(1)	19(1)	17(1)	-2(1)	2(1)	-2(1)
O(31')	20(1)	20(1)	20(1)	1(1)	3(1)	-1(1)
C(32')	19(1)	22(1)	23(1)	3(1)	-4(1)	1(1)
C(33')	33(2)	32(1)	36(2)	7(1)	10(1)	-2(1)
O(33')	32(1)	22(1)	36(1)	-5(1)	4(1)	-4(1)
C(4')	19(1)	19(1)	18(1)	0(1)	-2(1)	1(1)
O(41')	24(1)	20(1)	18(1)	2(1)	-3(1)	0(1)
C(42')	14(1)	29(1)	16(1)	1(1)	3(1)	1(1)
C(43')	28(1)	26(1)	23(1)	1(1)	-3(1)	0(1)
O(43')	28(1)	25(1)	22(1)	0(1)	-4(1)	-5(1)
C(5')	21(1)	17(1)	19(1)	-1(1)	0(1)	-1(1)
C(5)	24(1)	18(1)	19(1)	2(1)	1(1)	-4(1)
O(1)	27(1)	19(1)	26(1)	-2(1)	-3(1)	-3(1)
C(2)	38(2)	19(1)	23(1)	7(1)	-4(1)	-10(1)
O(21)	61(2)	23(1)	32(1)	-3(1)	-7(1)	-10(1)
S(3)	23(1)	40(1)	32(1)	-3(1)	-4(1)	-10(1)
N(4)	21(1)	30(1)	22(1)	-4(1)	0(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for publish.

	x	y	z	U(eq)
H(11')	8229	4179	4435	26
H(131')	5903	6440	6104	54
H(132')	7536	6837	5751	54
H(133')	5988	7044	5229	54
H(21')	9548	4357	3200	24
H(231')	13412	4831	4931	51
H(232')	12289	5824	5100	51
H(233')	13287	5773	4263	51
H(31')	8542	6515	3149	22
H(331')	12086	7577	1371	41
H(332')	12388	6330	1510	41
H(333')	10984	6716	936	41
H(41')	7504	4885	2054	23
H(431')	5083	7112	352	32
H(432')	6681	7565	712	32
H(433')	5110	7723	1225	32
H(51')	5754	5784	3325	23

Appendix 4a:
5-(3-O-Benzoyl-1,2-O-isopropylidene-alpha-D-xylo-furanos-4-yl)-3-bromo-2-isoxazoline



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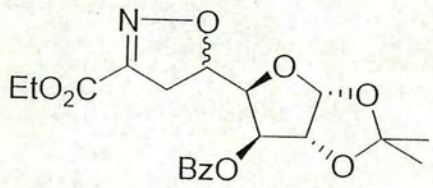
Appendix 4b:
5-(3-O-Benzoyl-1,2-O-isopropylidene-alpha-D-xylo-furanos-4-yl)-3-carbethoxy-2-isoxazoline



82

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RG 8
NS 800
TE 297

FW 3500
O2 0.0
DP 63L PO

LB -.200
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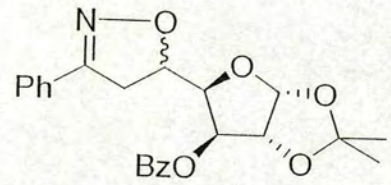
CY 0.0
F1 10.200P
F2 -.299P
HZ/CM 60.037
PPM/CM .300
SR 2342.89

pg 2

Appendix 4c:
5-(3-O-Benzoyl-1,2-O-isopropylidene-alpha-D-xylo-furanos-4-yl)-3-phenyl-2-isoxazoline



83

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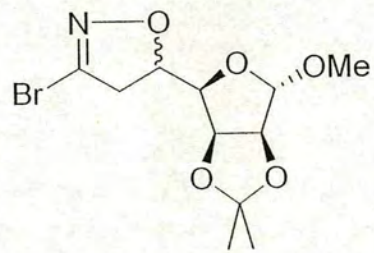
Appendix 4d:
3-Bromo-5-(methyl-1,2-O-isopropylidene-alpha-D-lyxo-furanos-4-yl)-2-isoxazoline



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KG XVI - 1H spectrum

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PROCNO 1

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DS 2
SWH 4310.345 Hz
FIDRES 0.131541 Hz
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RG 128
DW 116.000 usec
DE 6.00 usec
TE 300.0 K
D1 0.20000000 sec
P1 12.50 usec
SFO1 360.1319807 MHz
NUC1 1H
PL1 3.00 dB

F2 - Processing parameters
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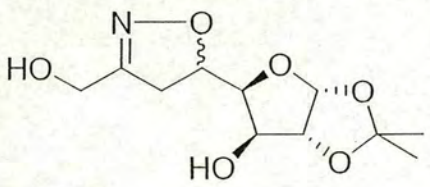
Appendix 4e:
Reduction Products 4eq. $NaBH_4$



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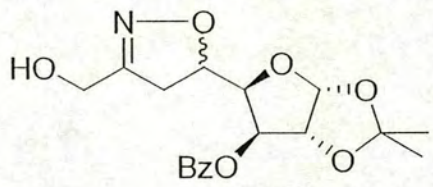

91

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ppm

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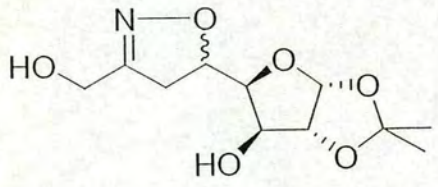
Appendix 4f:
Reduction Products 20 eq. $NaBH_4$



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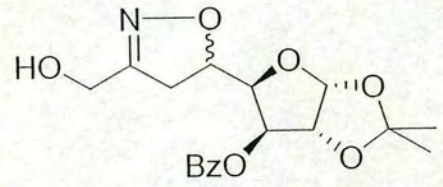

91

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AQ 3.8339059 sec
RG 4096
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DE 167.14 usec
TE 300.0 K
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P1 11.00 usec
SFO1 250.1316250 MHz
NUCLEUS 1H

F2 - Processing parameters
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SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
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F1 3001.56 Hz
F2P -0.500 ppm
F2 -125.06 Hz
PPMCM 0.37879 ppm/cm
HZCM 94.74619 Hz/cm